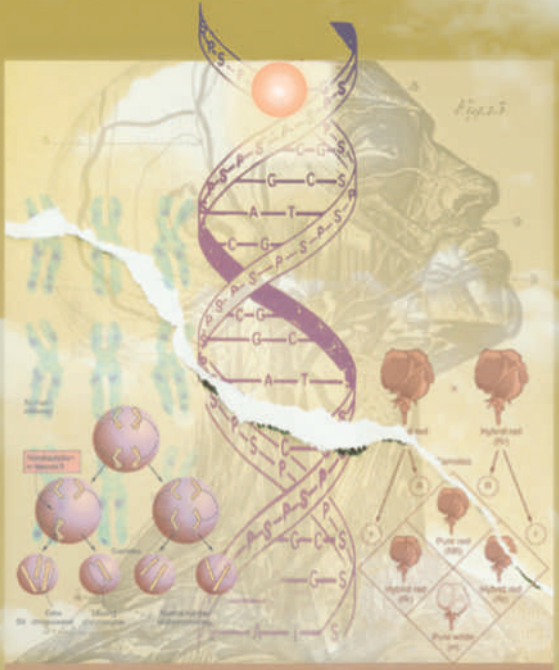
The GALE ENCYCLOPEDIA of GENETIC DISORDERS



STACEY L. BLACHFORD, EDITOR

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VOLUME

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STACEY L. BLACHFORD, EDITOR

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The GALE ENCYCLOPEDIA *of* GENETIC DISORDERS

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CONTENTS

PLEASE READ—IMPORTANT INFORMATION

The *Gale Encyclopedia of Genetic Disorders* is a medical reference product designed to inform and educate readers about a wide variety of disorders, conditions, treatments, and diagnostic tests. Gale Group believes the product to be comprehensive, but not necessarily definitive. It is intended to supplement, not replace, consultation with a physician or other health care practitioner. While Gale Group has made substantial efforts to provide information that is accurate, comprehensive, and up-to-date, the Gale Group makes no representations or warranties of any kind, including without limitation, warranties of merchantability or fitness for a particular purpose, nor does it guarantee the accuracy, comprehensiveness, or timeliness of the information contained in this product. Readers should be aware that the universe of medical knowledge is constantly growing and changing, and that differences of medical opinion exist among authorities. They are also advised to seek professional diagnosis and treatment for any medical condition, and to discuss information obtained from this book with their health care provider.

INTRODUCTION

The *Gale Encyclopedia of Genetic Disorders* is a unique and invaluable source for information regarding diseases and conditions of a genetic origin. This collection of nearly 400 entries provides in-depth coverage of disorders ranging from exceedingly rare to very well-known. In addition, several non-disorder entries have been included to facilitate understanding of common genetic concepts and practices such as Chromosomes, Genetic counseling, and Genetic testing.

This encyclopedia avoids medical jargon and uses language that laypersons can understand, while still providing thorough coverage of each disorder medical professionals will find beneficial as well. The *Gale Encyclopedia of Genetic Disorders* fills a gap between basic consumer health resources, such as single-volume family medical guides, and highly technical professional materials.

Each entry discussing a particular disorder follows a standardized format that provides information at a glance. The rubric used was:

- Definition
- Description
- Genetic profile
- Demographics
- Signs and symptoms
- Diagnosis
- Treatment and management
- Prognosis
- Resources
- Key terms

INCLUSION CRITERIA

A preliminary list of diseases and disorders was compiled from a wide variety of sources, including professional medical guides and textbooks, as well as consumer guides and encyclopedias. The advisory board, made up of seven medical and genetic experts, evaluated the topics and made suggestions for inclusion. Final selection of topics to include was made by the advisory board in conjunction with Gale Group editors.

ABOUT THE CONTRIBUTORS

The essays were compiled by experienced medical writers, primarily genetic counselors, physicians, and other health care professionals. The advisors reviewed the completed essays to insure they are appropriate, up-to-date, and medically accurate.

HOW TO USE THIS BOOK

The *Gale Encyclopedia of Genetic Disorders* has been designed with ready reference in mind.

- Straight **alphabetical arrangement** of topics allows users to locate information quickly.
- **Bold-faced terms** direct the reader to related articles.
- **Cross-references** placed throughout the encyclopedia point readers to where information on subjects without entries may be found.
- A list of **key terms** are provided where appropriate to define unfamiliar terms or concepts. Additional terms may be found in the **glossary** at the back of volume 2.
- The **Resources** section directs readers to additional sources of medical information on a topic.
- Valuable **contact information** for organizations and support groups is included with each entry. The appendix contains an extensive list of organizations arranged in alphabetical order.
- A comprehensive **general index** guides readers to all topics and persons mentioned in the text.

GRAPHICS

The *Gale Encyclopedia of Genetic Disorders* contains over 200 full color illustrations, including photos

and pedigree charts. A complete **symbol guide** for the pedigree charts can be found in the appendix.

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ADVISORY BOARD

An advisory board comprised of genetic specialists from a variety of backgrounds provided invaluable assistance in the formulation of this encyclopedia. This advisory board performed a myriad of duties, from defining the scope of coverage to reviewing individual entries for accuracy and accessibility. We would therefore like to express our sincere thanks and appreciation for all of their contributions.

CONTRIBUTORS

Christine Adamec
Medical Writer
Palm Bay, FL

Margaret Alic, PhD
Science Writer
Eastsound, WA

Lisa Andres, MS CGC
Certified Genetic Counselor
Medical Writer
San Jose, CA

Greg Annussek
Medical Writer/Editor
New York, NY

Sharon Aufox, MS CGC
Genetic Counselor
Rockford Memorial Hospital
Rockford, IL

Deepti Babu, MS
Genetic Counselor
Marshfield Clinic
Marshfield, WI

Kristin Baker Niendorf, MS CGC
Genetic Counselor
Massachusetts General Hospital
Boston, MA

Carin Lea Beltz, MS CGC
Genetic Counselor and Program Director
The Center for Genetic Counseling
Indianapolis, IN

Abdel Hakim Ben Nasr, PhD
Medical Writer
Dept. of Genetics
Yale University School of Medicine
New Haven, CT

Tanya Bivins, BS
Nursing Student
Madonna University
Livonia, MI

Bethanne Black
Medical Writer
Atlanta, GA

Jennifer Bojanowski, MS CGC
Genetic Counselor
Children's Hospital Oakland
Oakland, CA

Shelly Q. Bosworth, MS CGC
Genetic Counselor
Eugene, OR

Michelle L. Brandt
Medical Writer
San Francisco, CA

Dawn Cardeiro, MS CGC
Genetic Counselor
Fairfield, PA

Suzanne M. Carter, MS CGC
Senior Genetic Counselor
Clinical Coordinator
Montefiore Medical Center
Bronx, NY

Pamela E. Cohen, MS CGC
Genetic Counselor
San Francisco, CA

Randy Colby, MD
Senior Medical Genetics Fellow
Greenwood Genetic Center
Greenwood, SC

Sonja Eubanks, MS CGC
Genetic Counselor
Division of Maternal-Fetal Medicine
University of North Carolina at Chapel Hill
Chapel Hill, NC

David B. Everman, MD
Clinical Geneticist
Greenwood Genetic Center
Greenwood, SC

L. Fleming Fallon, Jr., MD DrPH
Associate Professor of Public Health
Bowling Green State University
Bowling Green, OH

Antonio Farina, MD PhD
Medical Writer
Dept. of Embryology
University of Bologna
Italy

Kathleen Fergus, MS
Genetic Counselor/Medical Writer
San Francisco, CA

Lisa Fratt
Medical Writer
Ashland, WI

Sallie B. Freeman, PhD
Assistant Professor
Dept. of Genetics
Emory University
Atlanta, GA

Mary E. Freivogel, MS
Account Executive
Myriad Genetic Laboratories, Inc.
Salt Lake City, UT

Rebecca Frey, PhD
Consulting Editor
East Rock Institute
Yale University
New Haven, CT

Sandra Galeotti, MS
Medical Writer
Sau Paulo, Brazil

Avis L. Gibons
Genetic Counseling Intern
UCI Medical Center
Orange, CA

Taria Greenberg, MHS
Medical Writer
Houston, TX

David E. Greenberg, MD
Medicine Resident
Baylor College of Medicine
Houston, TX

Benjamin M. Greenberg
Medical Student
Baylor College of Medicine
Houston, TX

Farris Farid Gulli, MD
Plastic and Reconstructive Surgery
Farmington Hills, MI

Judy C. Hawkins, MS
Genetic Counselor
The University of Texas Medical Branch
Galveston, TX

David Helwig
Medical Writer
London, ON, Canada

Edward J. Hollox, PhD
Medical Writer
Institute of Genetics, Queen's Medical Center
University of Nottingham
Nottingham, England

Katherine S. Hunt, MS
Genetic Counselor
University of New Mexico Health Sciences Center
Albuquerque, NM

Cindy Hunter, MS CGC
Genetic Counselor
Medical Genetics Department
Indiana University School of Medicine
Indianapolis, IN

Kevin Hwang, MD
Medical Writer
Morristown, NJ

Holly A. Ishmael, MS CGC
Genetic Counselor
The Children's Mercy Hospital
Kansas City, MO

Dawn A. Jacob, MS
Genetic Counselor
Obstetrix Medical Group of Texas
Fort Worth, TX

Paul A. Johnson
Medical Writer
San Diego, CA

Melissa Knopper
Medical Writer
Chicago, IL

Terri A. Knutel, MS CGC
Genetic Counselor
Chicago, IL

Karen Krajewski, MS CGC
Genetic Counselor
Assistant Professor of Neurology
Wayne State University
Detroit, MI

Sonya Kunkle
Medical Writer
Baltimore, MD

Renée Laux, MS
Certified Genetic Counselor
Eastern Virginia Medical School
Norfolk, VA

Marshall Letcher, MA
Science Writer
Vancouver, BC

Christian L. Lorson, PhD
Assistant Professor
Dept. of Biology
Arizona State University
Tempe, AZ

Maureen Mahon, BSc MFS
Medical Writer
Calgary, AB

Nicole Mallory, MS
Medical Student
Wayne State University
Detroit, MI

Ron C. Michaelis, PhD FACMG
Research Scientist
Greenwood Genetic Center
Greenwood, SC

Bilal Nasser, MSc
Senior Medical Student
Universidad Iberoamericana
Santo Domingo, Domincan Republic

Jennifer E. Neil, MS CGC
Genetic Counselor
Long Island, NY

Pamela J. Nutting, MS CGC
Senior Genetic Counselor
Phoenix Genetics Program
University of Arizona
Phoenix, AZ

Marianne F. O'Connor, MT (ASCP) MPH
Medical Writer
Farmington Hills, MI

Barbara Pettersen, MS CGC
Genetic Counselor
Genetic Counseling of Central Oregon
Bend, OR

Toni Pollin, MS CGC
Research Analyst
Division of Endocrinology, Diabetes, and Nutrition
University of Maryland School of Medicine
Baltimore, MD

Scott J. Polzin, MS CGC
Medical Writer
Buffalo Grove, IL

Nada Quercia, Msc CCGC CGC
Genetic Counselor
Division of Clinical and Metabolic Genetics
The Hospital for Sick Children
Toronto, ON, Canada

Robert Ramirez, BS
Medical Student
University of Medicine & Dentistry of New Jersey
Stratford, NJ

Julianne Remington
Medical Writer
Portland, OR

Jennifer Roggenbuck, MS CGC
Genetic Counselor
Hennepin County Medical Center
Minneapolis, MN

Edward R. Rosick, DO MPH MS
University Physician/Clinical Assistant Professor
The Pennsylvania State University
University Park, PA

Judyth Sassoon, ARCS PhD
Medical Writer
Dept. of Chemistry and Biochemistry
University of Bern
Bern, Switzerland

Jason S. Schliesser, DC
Chiropractor
Holland Chiropractic, Inc.
Holland, OH

Charles E. Schwartz, PhD
Director of Center for Molecular Studies
JC Self Research Center
Greenwood Genetic Center
Greenwood, SC

Laurie H. Seaver, MD
Clinical Geneticist
Greenwood Genetic Center
Greenwood, SC

Nina B. Sherak, MS CHES
Health Educator/Medical Writer
Wilmington, DE

Genevieve Slomski, PhD
Medical Writer
New Britain, CT

Java O. Solis, MS
Medical Writer
Decatur, GA

Amie Stanley, MS
Genetic Counselor
University of Florida
Gainesville, FL

Constance K. Stein, PhD
Director of Cytogenetics
Assistant Director of Molecular Diagnostics
SUNY Upstate Medical University
Syracuse, NY

Kevin M. Sweet, MS CGC
Cancer Genetic Counselor
James Cancer Hospital
Ohio State University
Columbus, OH

Catherine Tesla, MS CGC
Senior Associate, Faculty
Dept. of Pediatrics, Division of Medical Genetics
Emory University School of Medicine
Atlanta, GA

Oren Traub, MD PhD
Resident Physician
Dept. of Internal Medicine
University of Washington Affiliated Hospitals
Seattle, WA

Amy Vance, MS CGC
Genetic Counselor
GeneSage, Inc.
San Francisco, CA

Brian Veillette, BS
Medical Writer
Auburn Hills, MI

Linnea E. Wahl, MS
Medical Writer
Berkeley, CA

Ken R. Wells
Freelance Writer
Laguna Hills, CA

Jennifer F. Wilson, MS
Science Writer
Haddonfield, NJ

Philip J. Young, PhD
Research Fellow
Dept. of Biology
Arizona State University
Tempe, AZ

Michael V. Zuck, PhD
Medical Writer
Boulder, CO

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4p minus syndrome *see* **Wolf-Hirschhorn syndrome**

5p deletion syndrome *see* **Cri du chat syndrome**

5p minus syndrome *see* **Cri du chat syndrome**

22q1 deletion syndrome *see* **Deletion 22q1 syndrome**

47,XXY syndrome *see* **Klinefelter syndrome**

Aarskog syndrome

Definition

Aarskog syndrome is an inherited disorder that causes a distinctive appearance of the face, skeleton, hands and feet, and genitals. First described in a Norwegian family in 1970 by the pediatrician Dagfinn Aarskog, the disorder has been recognized worldwide in most ethnic and racial groups. Because the responsible **gene** is located on the X chromosome, Aarskog syndrome is manifest almost exclusively in males. The prevalence is not known.

Description

Aarskog syndrome is among the **genetic disorders** with distinctive patterns of physical findings and is confused with few others. Manifestations are present at birth allowing for early identification. The facial appearance and findings in the skeletal system and genitals combine to make a recognizable pattern. The diagnosis is almost exclusively based on recognition of these findings. Although the responsible gene has been identified, testing for gene mutations is available only in research laboratories. Aarskog syndrome is also called Faciogenital dysplasia, Faciogenitodigital syndrome, and Aarskog-Scott syndrome.

Genetic profile

Aarskog syndrome is caused by mutations in the FGD1 gene, located on the short arm of the X chromosome (Xp11.2). In most cases, the altered gene in affected males is inherited from a carrier mother. Since males have a single X chromosome, mutations in the FGD1 gene produces full expression in males. Females who carry a mutation of the FGD1 gene on one of their two X **chromosomes** are usually unaffected, but may have subtle facial differences and less height than other females in the family.

Female carriers have a 50/50 chance of transmitting the altered gene to daughters and each son. Affected males are fully capable of reproduction. They transmit their single X chromosome to all daughters who, therefore, are carriers. Since males do not transmit their single X chromosome to sons, all sons are unaffected.

The gene affected in Aarskog FGD1 codes for a Rho/Rac guanine exchange factor. While the gene product is complex and the details of its function are incompletely understood, it appears responsible for conveying messages within cells that influence their internal architecture and the activity of specific signal pathways. However, the precise way in which mutations in FGD1 produce changes in facial appearance and in the skeletal and genital systems is not yet known.

Demographics

Only males are affected with Aarskog syndrome, although carrier females may have subtle changes of the facial structures and be shorter than noncarrier sisters. There are no high risk racial or ethnic groups.

KEY TERMS

Rho/Rac guanine exchange factor—Member of a class of proteins that appear to convey signals important in the structure and biochemical activity of cells.

Signs and symptoms

Manifestations of Aarskog syndrome are present from birth. The facial appearance is distinctive and in most cases is diagnostic. Changes are present in the upper, middle, and lower portion of the face. Increased width of the forehead, growth of scalp hair into the middle of the forehead (widow's peak), increased space between the eyes (ocular hypertelorism), a downward slant to the eye openings, and drooping of the upper eyelids (ptosis) are the major features in the upper part of the face. A short nose with forward-directed nostrils and simply formed small ears that may protrude are the major findings in the mid-part of the face. The mouth is wide and the chin small. As the face elongates in adult life, the prominence of the forehead and the increased space between the eyes becomes less apparent. Dental abnormalities include slow eruption, missing teeth, and broad upper incisors.

The fingers are often held in a distinctive position with flexion at the joint between the hand and the fingers, over extension at the first joint of the finger and flexion at the second joint. This hand posturing becomes more obvious when there is an attempt to spread the fingers. There may also be some mild webbing between the fingers. The fingers are short and there is often only a single crease across the middle of the palm. The toes are also short and the foot is often bent inward at its middle portion. All of the joints may be unusually loose. Excessive movement of the cervical spine may lead to impingement on the spinal cord. In some cases, the sternum (breastbone) may appear depressed (pectus excavatum).

Changes in the appearance of the genitals may also be helpful in diagnosis. One or both testes may remain in the abdomen, rather than descending into the scrotal sac. The scrotum tends to surround the penis giving a so-called "shawl scrotum" appearance. Hernias may appear in the genital and umbilical regions. Linear growth in childhood and adult height are generally less than in unaffected brothers. The head size is usually normal.

Although most affected males have normal intellectual function, some individuals will have mild impairments. There does not appear to be any particular association with behavioral disturbances. However, attention deficit occurs among some boys with learning difficulties.

Diagnosis

The diagnosis of Aarskog syndrome is made on the basis of clinical findings, primarily analysis of the family history and characteristic facial, skeletal, and genital findings. There are no laboratory or radiographic changes that are specific. Although the diagnosis can be confirmed by finding a mutation in the FGD1 gene, this type of testing is available only in research laboratories.

In families with a prior occurrence of Aarskog syndrome, prenatal diagnosis might be possible through ultrasound examination of the face, hands, and feet, or by testing the FGD1 gene. However, this is not generally sought since the condition is not considered medically severe.

Few other conditions are confused with Aarskog syndrome. **Noonan syndrome**, another single gene disorder that has short stature, ocular hypertelorism, downslanting eye openings, and depression of the lower chest, poses the greatest diagnostic confusion. Patients with Noonan syndrome often have wide necks and heart defects, which is helpful in distinguishing them from patients with Aarskog syndrome.

The older patient may pose greater difficulty due to loss of facial findings and obscuring of shawl scrotum by pubic hair.

As in many disorders, there is a range of severity of the clinical appearance even within the same family. In these cases, examination of several affected family members and attention to family history may be helpful.

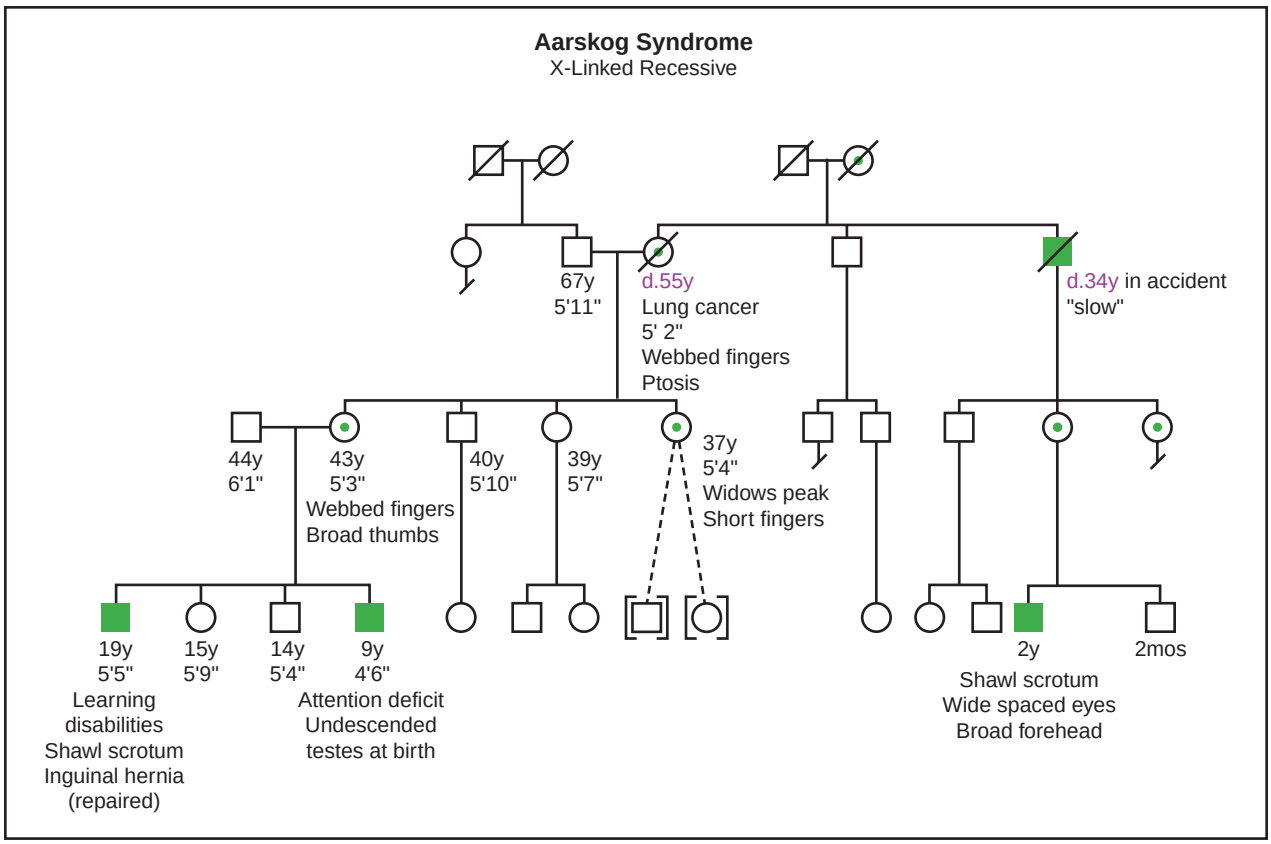
Treatment and management

Since there are no major malformations or major mental disabilities in Aarskog syndrome, the diagnosis may be reassuring. Developmental milestones and school progress should be monitored, as there may be impairment of intellectual function in some individuals.

The X-linked **inheritance** pattern should be described to the family.

Prognosis

Short-term and long-term prognosis is favorable. Life threatening malformations or other health concerns rarely occur. Special educational attention may be necessary for those with learning difficulties. A minority of affected persons will have spinal cord compression, usu-



(Gale Group)

ally in the neck, causing pain or injury to peripheral nerves. Neurosurgical intervention is necessary in some cases. Hernias in the umbilical and groin areas may be surgically repaired.

Resources

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ORGANIZATIONS

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Roger E. Stevenson, MD

Aase syndrome

Definition

Aase syndrome is a rare, autosomal recessive genetic disorder characterized by congenital hypoplastic anemia (CHA) and triphalangeal thumbs (TPT). People with Aase syndrome may have one or more physical abnormalities. Poor growth in childhood is common, but mental retardation and other neurological problems are not associated with Aase syndrome.

Description

Aase syndrome is sometimes also called Aase–Smith syndrome, or Congenital Anemia–Triphalangeal Thumb syndrome. It is a very rare hereditary syndrome involving multiple birth defects. The two symptoms that must be present to consider the diagnosis of Aase syndrome are CHA and TPT. CHA is a significant reduction from birth in the number of red cells in the blood. TPT means that one or both thumbs have three bones (phalanges) rather than the normal two.

KEY TERMS

Blackfan-Diamond syndrome (BDS)—A disorder with congenital hypoplastic anemia. Some researchers believe that some or all individuals with Aase syndrome actually have BDS, that Aase syndrome and BDS are not separate disorders.

Congenital hypoplastic anemia (CHA)—A significant reduction in the number of red blood cells present at birth, usually referring to deficient production of these cells in the bone marrow. Also sometimes called congenital aplastic anemia.

Fontanelle—One of several "soft spots" on the skull where the developing bones of the skull have yet to fuse.

Hypoplastic radius—Underdevelopment of the radius, the outer, shorter bone of the forearm.

Triphalangeal thumb (TPT)—A thumb that has three bones rather than two.

Several other physical abnormalities have been described in individuals with Aase syndrome, including narrow shoulders, hypoplastic radius (underdevelopment of one of the bones of the lower arm), heart defect, cleft lip/palate, and late closure of the fontanelles (soft spots on an infant's skull where the bones have not yet fused). The specific cause of Aase syndrome is not known, but recurrence of the condition in siblings implies an abnormal **gene** is responsible.

Genetic profile

The available evidence suggests Aase syndrome is inherited in an autosomal recessive fashion meaning that an affected person has two copies of an abnormal gene. Parents of an affected individual carry one abnormal copy of that particular gene, but their other gene of the pair is normal. One copy of the normal gene is sufficient for the parent to be unaffected. If both parents are carriers of a gene for the same autosomal recessive condition, there is a one in four chance in each pregnancy that they will both pass on the abnormal gene and have an affected child.

Autosomal recessive inheritance is suspected for Aase syndrome based on the pattern seen in the families that have been described. An autosomal recessive pattern requires that only siblings are affected by the condition (parents are unaffected gene carriers), and the disorder occurs equally in males and females. As of 2000, an abnormal gene proven to cause Aase syndrome had not been discovered.

Demographics

Aase syndrome is quite rare, with possibly no more than two dozen cases reported in the medical literature.

Signs and symptoms

CHA and TPT are the two classic signs of Aase syndrome. The anemia may require treatment with steroids, or possibly blood transfusions, but tends to improve over time. TPT may cause a person with Aase syndrome to have difficulty grasping and manipulating objects with their hands. A hypoplastic radius may complicate problems with appearance and movement of the hands and arms. Narrow and sloping shoulders are caused by abnormal development of the bones in that area of the body.

Slow growth in children with Aase syndrome may be partly related to their anemia, but is more likely to be genetically predetermined due to the syndrome. Ventricular septal defect (VSD), a hole between the bottom two chambers of the heart, is the cardiac defect reported most often, and several cases of **cleft lip and palate** have occurred as well.

Diagnosis

The diagnosis of Aase syndrome is made when an infant has CHA and TPT, and one or more of the other symptoms. Children with another more common congenital anemia syndrome, Blackfan–Diamond syndrome (BDS), sometimes have abnormalities of their thumbs. Since the syndromes have overlapping symptoms, there is some question about whether Aase syndrome and BDS are contiguous gene syndromes or even identical conditions. Further genetic research may resolve this issue.

Treatment and management

Anemia associated with Aase syndrome is often helped by the use of a steroid medication. For serious anemia that does not respond to medications, blood transfusions from a matched donor might be necessary. Management of problems related to the skeletal abnormalities should be treated by orthopedic surgery as well as physical and occupational therapy. Heart defects and cleft lip and palate are nearly always correctable, but both require surgery and long–term follow up. A genetic evaluation and counseling should be offered to any individual

or couple whose child is suspected of having Aase syndrome.

Prognosis

While major medical procedures such as blood transfusions and corrective surgeries might be needed for a child with Aase syndrome, the long–term prognosis seems to be good. Discovery of the specific genetic defect is not likely to immediately change the prognosis. Development of a reliable genetic test, however, might allow for carrier testing for other family members, and prenatal diagnosis for couples who already have an affected child.

Resources

ORGANIZATIONS

Aicardi Syndrome Awareness and Support Group. 29 Delavan Ave., Toronto, ON M5P 1T2 Canada. (416) 481-4095.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Heart, Lung, and Blood Institute. PO Box 30105, Bethesda, MD 20824-0105. (301) 592-8573. nhlbiinfo@rover.nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. <http://www.nsgc.org/GeneticCounselingYou.asp>.

Scott J. Polzin, MS, CGC

Aase-Smith syndrome *see* **Aase syndrome**

Abetalipoproteinemia

Definition

Abetalipoproteinemia (ABL) is a rare inherited disorder characterized by difficulty in absorbing fat during digestion. The result is absence of betalipoproteins in the blood, abnormally shaped red blood cells, and deficiencies of vitamins A, E, and K. Symptoms include intestinal, neurological, muscular, skeletal, and ocular problems, along with anemia and prolonged bleeding in some cases.

Description

An unusual sign first described in ABL is the presence of star-shaped red blood cells, which were dubbed "acanthocytes" (literally, *thorny cells*). Thus, ABL is also known by the name acanthocytosis. Less commonly, ABL may be referred to as Bassen-Kornzweig syndrome.

The underlying problem in ABL is a difficulty in absorbing fats (lipids) in the intestine. Most people with ABL first develop chronic digestive problems, and then progress to neurological, muscular, skeletal, and ocular disease. Disorders of the blood may also be present. Severe vitamin deficiency causes many of the symptoms in ABL. Treatments include restricting fat intake in the diet and vitamin supplementation. Even with early diagnosis and treatment, though, ABL is progressive and cannot be cured.

Genetic profile

Fats are important components of a normal diet, and their processing, transport, and use by the body are critical to normal functioning. Lipids bind to protein (lipoprotein) so they can be absorbed in the intestine, transferred through the blood, and taken up by cells and tissues throughout the body. There are many different lipoprotein complexes in the body. One group, the betalipoproteins, must combine with another protein, microsomal triglyceride transfer protein (MTP). ABL is caused by abnormalities in the **gene** that codes for MTP. When MTP is nonfunctional or missing, then betalipoproteins will also be decreased or absent. The MTP gene has been localized to chromosome 4.

ABL is an autosomal recessive genetic disorder. This means that both copies of the MTP gene are abnormal in a person affected with the disorder. Since all genes are present at conception, a person cannot "acquire" ABL. Each parent of an affected child carries the abnormal MTP gene but also has a normally functioning gene of that pair. Enough functional MTP is produced by the normal gene so that the parent is unaffected (carrier). When both parents are carriers of the same recessive gene, there is a one in four chance in each pregnancy that they will have an affected child.

Demographics

ABL is rare, and the true incidence of the disorder is unknown. Prior to the description of ABL in 1950, it is

KEY TERMS

Acanthocytosis—The presence of acanthocytes in the blood. Acanthocytes are red blood cells that have the appearance of thorns on their outer surface.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Chylomicron—A type of lipoprotein made in the small intestine and used for transporting fats to other tissues in the body. MTP is necessary for the production of chylomicrons.

Clubfoot—Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

Consanguinity—A mating between two people who are related to one another by blood.

Lipoprotein—A lipid and protein chemically bound together, which aids in transfer of the lipid in and out of cells, across the wall of the intestine, and through the blood stream.

Low density lipoproteins (LDL)—A cholesterol carrying substance that can remain in the blood stream for a long period of time.

Neuromuscular—Involving both the muscles and the nerves that control them.

Ocular—A broad term that refers to structure and function of the eye.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

Triglycerides—Certain combinations of fatty acids (types of lipids) and glycerol.

Vitamin deficiency—Abnormally low levels of a vitamin in the body.

believed that people with ABL were diagnosed as having either **Friedreich ataxia** (a more common form of hereditary ataxia) or some other neurologic disorder. Misdiagnosis may still occur if all of the symptoms are not present, or if they do not occur in a typical fashion. Most of the reported cases of ABL have been in the Jewish population, but individuals from other ethnic backgrounds have been described as well. As many as one-third of people with ABL have had genetically related (consanguineous) parents. Higher rates of consanguinity are often seen in rare autosomal recessive disorders.

Signs and symptoms

Too much fat left unabsorbed in the intestine results in the symptoms that are often noticed first in ABL, such as chronic diarrhea, loss of appetite, vomiting, and slow weight gain and growth due to reduced uptake of nutrients.

Various lipids, such as cholesterol and its components, are important in the development and normal functioning of nerve and muscle cells. Decreased lipid levels in the bloodstream, and thus elsewhere in the body, are partly responsible for the neuromuscular and ocular problems encountered in ABL. Neurological symptoms include ataxia (poor muscle coordination), loss of deep tendon reflexes, and decreased sensation to touch, pain, and temperature.

Muscular atrophy, the weakening and loss of muscle tissue, is caused by the decreased ability of nerves to control those muscles, as well as lack of nutrients for the muscles themselves. Weakened heart muscle (cardiomyopathy) may occur, and several severe cases have been reported that resulted in early death.

Retinitis pigmentosa is progressive, especially without treatment, and the typical symptoms are loss of night vision and reduced field of vision. Loss of clear vision, nystagmus (involuntary movement of the eyes), and eventual paralysis of the muscles that control the eye may also occur.

Skeletal problems associated with ABL include various types of curvature of the spine and clubfeet. The abnormalities of the spine and feet are thought to result from muscle strength imbalances in those areas during bone growth.

Severe anemia sometimes occurs in ABL, and may be partly due to deficiencies of iron and folic acid (a B vitamin) from poor absorption of nutrients. In addition, because of their abnormal shape, acanthocytes are prematurely destroyed in the blood stream.

Vitamins A, E, and K are fat soluble, meaning they dissolve in lipids in order to be used by the body. Low lipid levels in the blood means that people with ABL have chronic deficiencies of vitamins A, E, and K. Much of the neuromuscular disease seen in ABL is thought to be caused by deficiencies of these vitamins, especially vitamin E.

Approximately one-third of all individuals with ABL develop mental retardation. However, since the proportion of cases involving consanguinity is also reported to be about one-third, it is difficult to determine if mental retardation in individuals with ABL is due to the disease itself or to other effects of consanguinity. Consanguinity may also be responsible for other birth defects seen infrequently in ABL.

Diagnosis

The diagnosis of ABL is suspected from the intestinal, neuromuscular, and ocular symptoms, and is confirmed by laboratory tests showing acanthocytes in the blood and absence of betalipoproteins and chylomicrons in the blood. Other diseases resulting in similar intestinal or neurological symptoms, and those associated with symptoms related to malnutrition and vitamin deficiency must be excluded. As of 2000, there was no direct test of the MTP gene available for routine diagnostic testing. Accurate carrier testing and prenatal diagnosis are therefore not yet available. However, this could change at any time. Any couple whose child is diagnosed with ABL should be referred for **genetic counseling** to obtain the most up-to-date information.

Treatment and management

The recommended treatments for ABL include diet restrictions and vitamin supplementation. Reduced triglyceride content in the diet is suggested if intestinal symptoms require it. Large supplemental doses of vitamin E (tocopherol) have been shown to lessen or even reverse the neurological, muscular, and retinal symptoms in many cases. Supplementation with a water-soluble form of vitamin A is also suggested. Vitamin K therapy should be considered if blood clotting problems occur.

Occupational and physical therapy can assist with any muscular and skeletal problems that arise. Physicians that specialize in orthopedics, digestive disorders, and eye disease should be involved. Support groups and specialty clinics for individuals with multisystem disorders such as ABL are available in nearly all metropolitan areas.

Prognosis

ABL is rare, which means there have been few individuals on which to base prognostic information. The effectiveness of vitamin supplementation and diet restrictions will vary from person to person and family to family. Life span may be near normal with mild to moderate disability in some, but others may have more serious and even life-threatening complications. Arriving at the correct diagnosis as early as possible is important. However, this is often difficult in rare conditions such as ABL. Future therapies, if any, will likely focus on improving lipid absorption in the digestive tract. Further study of the MTP gene may lead to the availability of accurate carrier testing and prenatal diagnosis for some families.

Resources

ORGANIZATIONS

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Foundation for Jewish Genetic Diseases, Inc. 250 Park Ave., Suite 1000, New York, NY 10017. (212) 371-1030. <http://www.nfjgd.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. <http://www.nsgc.org/GeneticCounselingYou.asp>.

National Tay-Sachs and Allied Diseases Association. 2001 Beacon St., Suite 204, Brighton, MA 02135. (800) 906-8723. ntasd-Boston@worldnet.att.net. <http://www.ntsad.org>.

Scott J. Polzin, MS, CGC

Acanthocytosis *see* **Abetalipoproteinemia**

Acardia

Definition

Acardia is a very rare, serious malformation that occurs almost exclusively in monozygous twins (twins developing from a single egg). This condition results from artery to artery connections in the placenta causing a physically normal fetus to circulate blood for both itself and a severely malformed fetus whose heart regresses or is overtaken by the pump twin's heart.

Description

Acardia was first described in the sixteenth century. Early references refer to acardia as chorioangiopagus parasiticus. It is now also called twin reversed arterial perfusion sequence, or TRAP sequence.

Mechanism

Acardia is the most extreme form of twin-twin transfusion syndrome. Twin-twin transfusion syndrome is a pregnancy complication in which twins abnormally share blood flow from the umbilical artery of one twin to the umbilical vein of the other. This abnormal connection can cause serious complications including loss of the pregnancy.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Dizygotic—From two zygotes, as in non-identical, or fraternal twins. The zygote is the first cell formed by the union of sperm and egg.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term embryo is used prior to the third month.

Monozygotic—From one zygote, as in identical twins. The zygote is the first cell formed by the union of sperm and egg.

In acardiac twin pregnancies, blood vessels abnormally connect between the twins in the placenta. The placenta is the important interface of blood vessels between a mother and baby through which babies receive nutrients and oxygen. This abnormal connection forces the twin with stronger blood flow to pump blood for both, straining the heart of this "pump" twin. This abnormal connection causes the malformed twin to receive blood directly from the pump twin before this blood gathers new oxygen. The poorly deoxygenated blood from the normal twin as well as the pressure deficiency as a result of trying to serve both infants may be the cause of the other twin's malformations.

The acardiac twin

The acardiac twin is severely malformed and may be incorrectly referred to as a tumor. In 1902, a physician named Das established four categories of acardiac twins based on their physical appearance. There is controversy surrounding the use of these traditional four categories because some cases are complex and do not fit neatly into one of Das's four categories. These four traditional categories include acardius acephalus, amorphus, anceps, and acormus.

Acardius acephalus is the most common type of acardiac twin. These twins do not develop a head, but may have an underdeveloped skull base. They have legs, but do not have arms. On autopsy they are generally found to lack chest and upper abdominal organs.

Acardius amorphus appears as a disorganized mass of tissues containing skin, bone, cartilage, muscle, fat, and blood vessels. This type of acardiac twin is not recognizable as a human fetus and contains no recognizable human organs.

Acardius anceps is the most developed form of acardiac twin. This form has arms, legs, and a partially developed head with brain tissues and facial structures. This type of acardiac twin is associated with a high risk for complications in the normal twin.

Acardius acormus is the rarest type of acardiac twin. This type of acardiac twin presents as an isolated head with no body development.

Genetic profile

There is no single known genetic cause for acardia. In most cases, the physically normal twin is genetically identical to the acardiac twin. In these cases, physical differences are believed to be due to abnormal blood circulation.

Aneuploidy, or an abnormal number of **chromosomes**, has been seen in several acardiac twins, but is rare in the normal twins. Trisomy 2, the presence of three copies of human chromosome 2 instead of the normal two copies, has been reported in the abnormal twin of two pregnancies complicated by TRAP sequence in different women. For both of these pregnancies the pump twin had normal chromosome numbers. Since monozygotic twins are formed from a single zygote, scientists theorize that an error occurs early in cell division in only one of the two groups of cells formed during this process.

Demographics

TRAP is a rare complication of twinning, occurring only once in about every 35,000 births. Acardia is believed to complicate 1% of monozygotic twin pregnancies. Risks in triplet, quadruplet, and other higher order pregnancies are even higher. Monozygotic twinning in higher order pregnancies are more common in pregnancies conceived with in vitro fertilization (IVF), hence increased risk for TRAP sequence is also associated with IVF.

This condition has been documented over five centuries occurring in many countries and in different races. As of 2001, specific rates for recurrence are unknown. However, a mother who has had a pregnancy complicated by TRAP sequence is very unlikely to have another pregnancy with the same complication.

Two cases of acardia have been associated with maternal **epilepsy** and the use of anticonvusants. One report, in 1996, describes an acardiac twin pregnancy in

an epileptic mother who took primidone, a seizure medication, in the first trimester of her pregnancy. Another report, in 2000, describes an acardiac twin pregnancy in an epileptic mother who took a different seizure medication, oxcarbazepin.

Diagnosis

A mother carrying an acardiac twin pregnancy is not likely to have any unusual symptoms. An acardiac twin is most often found incidentally on prenatal ultrasound. No two acardiac twins are formed exactly alike, so they may present differently. During ultrasound, an acardiac twin may appear as tissue mass or it may appear to be a twin who has died in the womb. Acardia is always suspected when, on ultrasound, a twin once considered to be dead begins to move or grow, or there is visible blood flow through that twin's umbilical cord. In 50% of cases the acardiac twin has only two, instead of the normal three, vessels in the umbilical cord. A two vessel umbilical cord may also be found in some normal pregnancies.

Ultrasound diagnostic criteria for the acardiac twin usually include:

- absence of fetal activity
- no heart beat
- continued growth
- increasing soft tissue mass
- undergrowth of the upper torso
- normal growth of the lower trunk

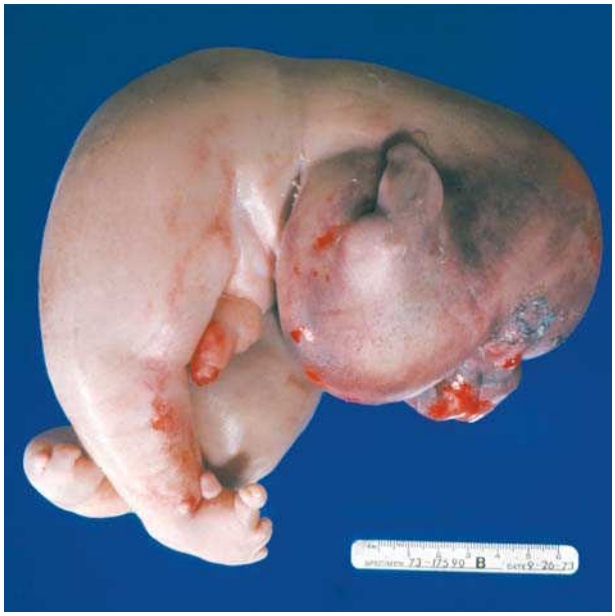
An acardiac fetus may also be missed on prenatal ultrasound. A 1991 report describes an acardiac twin who was missed on ultrasound and only detected at delivery. In rare cases a diagnosis of acardia is not possible until autopsy.

Treatment and management

As of 2001, there is no consensus on which therapy is best for pregnancies complicated by TRAP sequence. No treatment can save the acardiac twin, so the goal of prenatal therapy is to help the normal twin. The normal twin is not always saved by prenatal treatment.

Specialists have used laser and electrical cauterization, electrodes, serial **amniocentesis**, medications, and other treatments successfully. Physicians often recommend prenatal interruption of the blood vessel connections (thus sacrificing the acardiac twin) before heart failure develops in the pump twin.

Cutting off blood circulation to the acardiac twin can be accomplished by cauterizing or burning the blood vessel connections. In a 1998 study of seven pregnancies treated with laser therapy the rate of death in the normal twin was 13.6%, a vast improvement over the expected 50% death rate. Medications like digoxin may be used to treat congestive heart failure in the normal twin. Current studies examining the success and failure rates of these treatments will be helpful in determining which therapy is the best option.



This infant shows partial development of the lower extremities and early development of the head. Acardia almost always occurs in monozygotic twins, with one twin (such as that shown here) unable to fully develop as a result of severe heart complications. *(Greenwood Genetic Center)*

Fetal echocardiography is recommended to assist with early detection of heart failure in the normal twin. Chromosome studies are recommended for both fetuses in all pregnancies complicated by TRAP sequence.

Prognosis

The acardiac or parasitic twin never survives as it is severely malformed and does not have a functioning heart. Complications associated with having an acardiac twin cause 50–70% of normal twins to die. The normal twin is at risk for heart failure and complications associated with premature birth. Heart failure in the normal twin is common. The normal twin of an acardiac twin pregnancy has about a 10% risk for malformations. Therapy is thought to decrease the normal twin's risk for heart failure and premature birth. Improvement of therapies will undoubtedly lead to a better outlook for pregnancies complicated by TRAP sequence.

Resources

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Brassard, Myriam, et al. "Prognostic markers in twin pregnancies with an acardiac fetus." *Obstetrics and Gynecology* (September 1999): 409-14.

Mohanty, C., et al. "Acardiac anomaly spectrum." *Teratology* 62 (2000): 356- 359.

Rodeck, C., et al. "Thermocoagulation for the early treatment of pregnancy with an acardiac twin." *New England Journal of Medicine* 339 (1998): 1293-95.

ORGANIZATIONS

Twin Hope, Inc. 2592 West 14th St., Cleveland, OH 44113. (502) 243-2110. <http://www.twinhope.com>.

Judy C. Hawkins, MS

Accutane embryopathy

Definition

Accutane is commonly used to treat severe acne that has not responded to other forms of treatment. Accutane embryopathy refers to the pattern of birth defects that may be caused in an embryo that is exposed to Accutane during pregnancy. Accutane-related birth defects typically include physical abnormalities of the face, ears, heart, and brain.

Description

Accutane is one of several man-made drugs derived from vitamin A. The generic name for Accutane is *isotretinoin*. Accutane and other vitamin A-derivatives are referred to as *retinoids*. Vitamin A is an essential nutrient for normal growth and development. It is found in foods such as green leafy and yellow vegetables, oranges, pineapple, cantaloupe, liver, egg yolks, and butter. It is also available in multivitamins and separately as a daily supplement. Vitamin A is important in a number of biological processes. Included among these is the growth and differentiation of the epithelium, the cells that form the outer layer of skin as well as some of the layers beneath. Deficiency of vitamin A may lead to increased susceptibility to infection and problems with vision and growth of skin cells. The potential risks of supplemental vitamin A in a person's diet have been a matter of some debate. However, excess vitamin A during pregnancy does not seem to be associated with an increased risk for birth defects.

The same cannot be said for drugs derived from vitamin A. Accutane, like other retinoids, displays some of the same biologic properties as vitamin A, such as its role in stimulating the growth of epithelium. For this reason, it is an effective method of treatment for severe cases of nodular acne, a condition characterized by cystic, painful, scarring lesions. Four to five months of Accutane treatment usually leads to clearing of the acne for one year or more, even after the medicine is stopped. Accutane may also be prescribed for moderate acne that has not responded to other forms of treatment, usually antibiotics taken every day by mouth. Milder cases of acne that produce scarring or other related skin disorders may also be treated with this medication. Often, dermatologists prescribe Accutane only after other methods of treatment have been unsuccessful.

Common side effects of Accutane are chapped lips, dry skin with itching, mild nosebleeds, joint and muscle pain, and temporary thinning of hair. **Depression**, including thoughts of suicide, has been reported more recently as another, much more serious, potential side effect. Severe acne on its own is associated with lower self-esteem. As of 2001, no studies have been published to try to determine if Accutane use somehow makes it more likely for a person to be depressed or to attempt suicide.

The United States Food and Drug Administration (FDA) approved the use of Accutane in September 1982. It had previously been shown to cause birth defects in animals. Consequently, its approval was granted with the provision that the drug label would describe its risk of causing birth defects. The patient information brochure also included information for women taking the medication about avoiding preganancy.

The first report of an infant with Accutane-related birth defects was published in 1983. At least ten additional cases were subsequently reported to the FDA and Centers for Disease Control (CDC). A pattern of birth defects involving the head, ears, face, and heart was identified. In 1985, Dr. Edward Lammer reviewed a total of 154 pregnancies exposed to Accutane. Each of the pregnancies had included use of the drug during the first three months of pregnancy. This period, referred to as the *first trimester*, is a critical and sensitive time during which all of the organs begin to develop. Chemical insults during this part of pregnancy often result in abnormal formation of internal organs with or without external abnormalities.

Each of the 154 pregnancies had been voluntarily reported to either the FDA or CDC. The pregnancy outcomes included 95 elective pregnancy terminations and 59 continuing pregnancies. Of these, twelve (20%) ended in a spontaneous pregnancy loss, or miscarriage. The remaining 47 pregnancies resulted in six stillborn infants

with obvious abnormalities, 18 live born infants with abnormalities, and 26 apparently normal babies. The abnormalities observed among the stillborn and living infants were similar, most frequently involving the head, face, heart, and central nervous system. Thus, use of Accutane during the first several months of pregnancy was shown to be associated with an increased risk of pregnancy loss (miscarriage or stillbirth) as well as with a significant risk of birth defects in living children. This pattern of abnormalities has since become known as Accutane embryopathy. The term retinoic acid embryopathy is also occasionally used to describe the same condition because other retinoids, such as Tegison (etretinate), have been associated with a similar pattern of birth defects. Tegison is commonly used to treat severe psoriasis and can cause birth defects even if stopped years before becoming pregnant.

Genetic profile

Accutane embryopathy (AE) is not an inherited or hereditary type of abnormality. Rather, it is caused by exposure of a developing embryo to the drug, Accutane, during the first trimester of pregnancy. Accutane is a well known, powerful **teratogen**, or agent that causes physical or mental abnormalities in an embryo. Use anytime after the fifteenth day after conception, or approximately four weeks of pregnancy dating from the first day of the mother's last menstrual period, is associated with a significantly increased risk for pregnancy loss or an infant with AE. The dose of Accutane is unimportant. If Accutane is stopped prior to conception, no increased risk for loss or birth defects is expected.

Demographics

The total number of women of reproductive age (15-44 years old) taking Accutane is unknown. However, since the 1990s, the overall number of prescriptions written for Accutane has increased over two hundred percent. Prescriptions are evenly divided between men and women, but women 30 years old or younger account for 80% of the patients among their sex.

A Dermatologic and Ophthalmic Drug Advisory Committee was convened at the FDA in September 2000. Patterns of Accutane use and the outcomes of Accutane-exposed pregnancies were presented at this meeting. Two overlapping sources of pregnancy data exist: one sponsored by the manufacturer of the drug, Roche Laboratories, and a second study maintained by the Slone Epidemiology Unit at the Boston University School of Public Health. Representatives from both institutions reviewed their outcome data up to that time. This data supports previous estimates of the frequency of AE.

A total of 1,995 exposed pregnancies have been reported between the years 1982 and 2000. These pregnancies have been voluntarily reported either directly to the manufacturer or to the Slone Survey. Although doctors have referred some, a majority of participating women obtained the appropriate phone numbers from the insert included with their medication. Elective terminations of pregnancy were performed in 1,214 pregnancies. Spontaneous pregnancy losses were reported in 213 pregnancies and 383 infants were delivered. Of these, 162, or 42%, were born with malformations consistent with AE.

The numbers from the Slone Survey, which began in 1989, represent a large subset of the data reported by Roche. Any woman to whom Accutane is prescribed is invited to contact and participate in the project. As of September 2000, the survey had identified a total of 1,019 pregnancies out of more than 300,000 women enrolled. Some women were already pregnant when they had started Accutane but others conceived while taking the drug. The pregnancy data allows for examination of the risk factors that lead to becoming pregnant as well as the pregnancy outcomes. Among the 1,019 pregnancies that occurred, 681 were electively terminated, 177 resulted in a spontaneous loss, and 117 infants were delivered. Only 60 of these infants were either examined or had medical records available to review. Eight of the 60 (13%) were diagnosed with AE. No information was available on the remaining 57 pregnancies.

Each couple in the general population has a background risk of 3–4% of having a child with any type of congenital birth defect. The medical literature has suggested a 25–35% risk of AE in infants exposed to Accutane prenatally. The combined Roche and Slone Survey data provided a risk of 42%. Although consistent with the medical literature, this slightly higher number probably reflects some bias in reporting. In other words, some mothers may report their pregnancy only after the birth of a child with AE. Normal births may go unreported. This type of retrospective analysis is not as helpful as prospective reporting in which pregnancies are enrolled before the outcome is known. To ensure objective reporting, the Slone Survey only enrolls their participants prospectively, ideally before the end of the first trimester of pregnancy. Even still, the Slone Survey estimates that it likely only has information on roughly 40% of all Accutane-exposed pregnancies.

Signs and symptoms

AE is characterized by a number of major and minor malformations. Each abnormality is not present in every affected individual.

Craniofacial

- Malformed ears. Abnormalities of the ears, when present, involve both ears but may show different levels of severity ranging from mild external abnormalities to a very small or missing ear.
- Underdevelopment of the skull and facial bones. This leads to a specific facial features including a sharply sloping forehead, small jaw (*micrognathia*), flattened bridge of the nose, and an abnormal size and/or placing of the eye sockets and eyes.

Heart

- Structural defects, most of which require surgery to correct.

Central nervous systerm

- **Hydrocephalus**, or abnormal accumulation of fluid within the brain. This is the most common type of brain abnormality and often is treated by placement of a shunt within the head to drain the fluid.
- Small head size (*microcephaly*)
- Structural or functional brain abnormalities
- Mild to moderate mental retardation or learning disabilities later in life. Either may be present even in the absence of physical abnormalities.

Other

- Abnormal or very small thymus gland
- Cleft palate, or opening in the roof of the mouth

Diagnosis

A diagnosis of AE is based on two pieces of information: (1) report of Accutane use by the mother during the first trimester of pregnancy, and (2) recognition of the physical abnormalities in an exposed infant. The latter is accomplished by a physical examination by a doctor familiar with AE. Special studies of the heart, such as ultrasound, may be required after delivery to determine the specific nature of any structural heart defect.

Prenatal diagnosis is theoretically possible armed with the knowledge of early pregnancy exposure. A prenatal ultrasound evaluation may detect abnormalities such as heart defects, hydrocephalus or microcephaly, or some craniofacial abnormalities. However, not all features of AE will be apparent even with ultrasound, and a careful examination after delivery is still indicated.

Treatment and management

The care of an infant with AE after delivery is primarily symptomatic. Infants with serious heart abnormalities will need to be evaluated by a heart specialist and may require surgery in order to survive. Infants with brain abnormalties, such as hydrocephalus, may require shunt placement soon after birth and monitoring by a brain surgeon on a regular basis. Ear malformations may be associated with hearing loss in affected children. Depending on the severity of the ear abnormality, sign language may be needed for communication. Some infants with very severe internal birth defects, particularly of the heart, may die at a young age.

Based on the features associated with AE and the long-term medical care that may be required, the focus of the manufacturer of Accutane has long been on the prevention of as many pregnancies as possible. Roche Laboratories has made numerous efforts since 1982 to achieve this, including periodic changes in the drug label and attempts to increase doctor and consumer awareness about the teratogenic nature of Accutane during pregnancy.

In 1988, Roche developed the Accutane Pregnancy Prevention Program (PPP). It was fully implemented in mid-1989. The goal of the PPP was to develop educational materials about Accutane for both patients and their doctors. A PPP kit included a consent form and a patient information brochure. Prescribing physicians were encouraged to obtain informed consent from all of their patients after a verbal discussion of the risks and benefits of the drug. Pregnancy tests were strongly encouraged prior to beginning treatment. The patient information brochure included information about, as well as a toll-free phone number for, the patient referral program sponsored by Roche. The program offered to reimburse women for the cost of a visit to their doctor to review effective methods of birth control. Finally, warnings about the risks associated with Accutane were printed directly on the box and the individual drug packages.

An Accutane tracking study was implemented to evaluate how often doctors were using the PPP kit and following other major components of the program. The results of the study revealed that many doctors were inclined to rely only on oral communication about Accutane with their patients rather than using each of the elements of the PPP kit. The patient brochure was frequently used but other components of the kit were considered inconvenient and too time-consuming. Both Roche and the FDA agreed that certain parts of the PPP needed strengthening.

Additional support came in the form of a report published in the CDC-sponsored periodical, *Morbidity and Mortality Weekly Report* (MMWR), in January 2000. A group of 23 women was identified in California, all of whom had taken Accutane while pregnant. During March 1999, a representative from the CDC interviewed a total

of 14 of these women in an attempt to learn why pregnancies exposed to Accutane continued to occur despite the efforts of the PPP. Five women had electively terminated their pregnancies and had no information on whether birth defects had been present in the fetus. Four women experienced a spontaneous pregnancy loss, and four infants were born without obvious abnormalities. The last infant was born with features of AE, including a complex heart defect, hydrocephalus, and abnormal facial features. He subsequently died at the age of nine weeks.

Of greater interest to the authors, however, were some of the factors that contributed to the occurrence of these pregnancies in the first place. Some of the women had obtained Accutane from a source other than their doctor, such as in another country or from an associate. Another woman reported using medication left over from a previous prescription. In other cases, the prescription was filled before a pregnancy test was performed (usually the woman was already pregnant) or was started before day two or three of her menstrual period.

In March 1999, Roche submitted plans to the FDA for its revised Targeted Pregnancy Prevention Program. Over the course of the year 2000, the Targeted PPP was put into place, and efforts were resumed to educate doctors and patients alike. In May 2000, the FDA approved a new label for all Accutane packages. The label now includes the following recommendations:

- Two independent pregnancy tests are required, one before treatment begins and the next on the second day of the next normal menstrual period or 11 days after the last unprotected act of sexual intercourse, whichever is later.
- The prescription cannot be filled without a report from a physician documenting a negative pregnancy test result.
- If treatment is started while a woman has her menstrual period, it should be started on the second to third day of her period.
- Only a one-month supply of the drug will be given at a time.
- Two reliable forms of birth control, one primary, another secondary, must be used at the same time before treatment starts, during treatment, and one month after treatment ends. Examples of a primary method of birth control include birth control pills, a history of a sterilization procedure, such as a tubal ligation or vasectomy, or other form of injectable or implantable birth control product. Examples of a secondary form of birth control include use of a diaphragm, condom, or cervical cap, each with spermicide.

KEY TERMS

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

Miscarriage—Spontaneous pregnancy loss.

Psoriasis—A common, chronic, scaly skin disease.

Stillbirth—The birth of a baby who has died sometime during the pregnancy or delivery.

Thymus gland—An endocrine gland located in the front of the neck that houses and tranports T cells, which help to fight infection.

- Monthly contraceptive and pregnancy counseling are required as is a monthly pregnancy test.

The FDAs Dermatologic and Ophthalmic Drug Advisory Committee additionally recommended that doctors and their patients participate in a mandatory Accutane registry. Such a registry would be used to track how well prescribers and patients follow the elements of the Targeted PPP, such as pregnancy tests, informed consent, and use of birth control. A similar system has been developed to regulate the use of the drug thalidomide, another powerful human teratogen. Additionally, a centralized database could be maintained to track the outcomes of all Accutane-exposed pregnancies. As of early 2001, such a registry had not yet been established.

The possibility of a registry has met with criticism from professional organizations such as the American Academy of Dermatology (AAD). Critics have charged that a mandatory registry system would restrict access to the drug, particularly for those individuals with severe acne who may live in rural areas or otherwise do not have access to a doctor who is a member of the registry. The AAD agrees that education about Accutane as well as its potential hazards and safe and responsible use of the drug are of utmost importance.

To date, none of the efforts put forth by the drug manufacturer or the medical community has been 100% effective. Pregnancies while women are taking Accutane are still occurring, and infants with AE are still being born. As highlighted by the recent MMWR report, establishment of a registry or other strict methods of control are still unlikely to completely eliminate the birth of children with AE. It is possible in some cases to obtain

Accutane without using the services of a knowledgeable physician. Also, many pregnancies are unplanned and unexpected. Since first trimester exposure to Accutane may have serious consequences, time is of the essence in preventing as many prenatal exposures as possible. Doctors and their patients need to be equally attentive to the prevention of pregnancies and, thus, the continuing births of children with AE.

Prognosis

Accutane is a safe and highly effective drug when used properly. However, Accutane embryopathy is a serious medical condition that is directly related to a mother's use of Accutane during the first trimester of her pregnancy. Although most individuals with AE will have a normal lifespan, others may die at a young age due to complex internal abnormalities. Mild or moderate mental handicap is common even when there are no obvious physical features of AE.

Resources

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American Academy of Dermatology. PO Box 4014, 930 N. Meacham Rd., Schaumburg, IL 60168-4014. (847) 330-0230. Fax: (847) 330-0050. <http://www.aad.org>.

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Terri A. Knutel, MS, CGC

Achondrogenesis

Definition

Achondrogenesis is a disorder in which bone growth is severely affected. The condition is usually fatal early in life.

Description

General description

The syndrome achondrogenesis results from abnormal bone growth and cartilage formation. It is considered a lethal form of infantile dwarfism. Dwarfism is a condition that leads to extremely short stature. In achondrogenesis, the abnormalities in cartilage formation lead to abnormalities in bone formation. The lethality of the disorder is thought to result from difficulty breathing, probably due to having a very small chest. Achondrogenesis usually results in a stillborn infant or very early fatality. Achondrogenesis can be subdivided into type 1 and type 2. Type 1 can further be subdivided into type 1A and type 1B. Types 1A and 1B are distinguished by microscopic differences in the cartilage and cartilage-forming cells. Cartilage-forming cells (chondrocytes) are abnormal in type 1A, whereas the cartilage matrix itself is abnormal in type 1B.

Previously, health care professionals had recognized achondrogenesis types 3 and 4, but those classifications have been abandoned. Types 3 and 4 are now considered to be slight variations of type 2 achondrogenesis. Types 1A, 1B, and type 2 all have different genetic causes, and that is one factor supporting the current classification.

Synonyms

Synonyms for achondrogenesis include chondrogenesis imperfecta, hypochondrogenesis, lethal neonatal dwarfism, lethal osteochondrodysplasia, and neonatal dwarfism. Achondrogenesis type 1A is also known as Houston-Harris type, achondrogenesis type 1B is also known as Fraccaro type chondrogenesis, and achondrogenesis type 2 is also known as Langer-Saldino type achondrogenesis or type 3 or type 4 achondrogenesis.

Genetic profile

As previously mentioned, achondrogenesis is currently divided into three distinct subtypes: type 1A, type 1B, and type 2. It appears that each subtype is caused by mutations in different genes.

The **gene** for type 1A has not yet been isolated, but it does follow an autosomal recessive pattern of **inheritance**.

Type 1B follows an autosomal recessive pattern of inheritance as well, but the gene has been isolated. It is the diastrophic dysplasia sulfate transporter gene (DTDST), which is located on the long arm of chromosome 5 (5q32-q33 specifically). Abnormalities in the DTDST gene result in abnormal sulfation of proteins, which is thought to result in disease.

The severity of mutation determines which disorder the patient will have. The most severe of these disorders is type 1B. Since both type 1A and 1B follow autosomal recessive patterns of inheritance, the chance of parents having another child with the disorder after having the first child is 25% for both disorders.

Similar to achondrogenesis type 1B, achondrogenesis type 2 represents the most severe disorder of a group of disorders resulting from the mutation of a single gene—the collagen type 2 gene (COL2A1), located on the long arm of chromosome 12 (12q13.1-q13.3 specifically). In addition to its important role in development and growth, collagen type 2 plays an important structural role in cartilage and in the ability of cartilage to resist compressive forces. Type 2, however, does not follow an autosomal recessive pattern of inheritance. Most of the mutations that cause type 2 are new mutations, meaning they are not passed from parents to children. Also, most of these mutations are considered autosomal dominant. However, some family members of affected children may have the mutant gene without having the disease. This is not a classical pattern of dominance and implies the involvement of other genes in the disease process.

Demographics

Achondrogenesis is equally rare in males and females of all races in the United States. Although the exact incidence is unknown, one estimate places the incidence at 1 case in every 40,000 births.

Signs and symptoms

Traits found in all subtypes of achondrogenesis

All infants with achondrogenesis share these characteristics: an extremely short neck, underdeveloped lungs, a protuberant abdomen, low birth weight, extremely short limbs (micromelia) and other skeletal abnormalities. The most defining feature of this condition is the extreme shortness of the limbs.

Additionally, fetuses with achondrogenesis may have the condition polyhydramnios, a condition in which there is too much fluid around the fetus in the amniotic sac, and/or fetal hydrops, a condition in which there is too much fluid in the fetal tissues and/or cavities. Infants with achondrogenesis are also often born in the breech position (hindquarters first).

KEY TERMS

Chondrocyte—A specialized type of cell that secretes the material which surrounds the cells in cartilage.

Fetal hydrops—A condition in which there is too much fluid in the fetal tissues and/or cavities.

Micromelia—The state of having extremely short limbs.

Ossification—The process of the formation of bone from its precursor, a cartilage matrix.

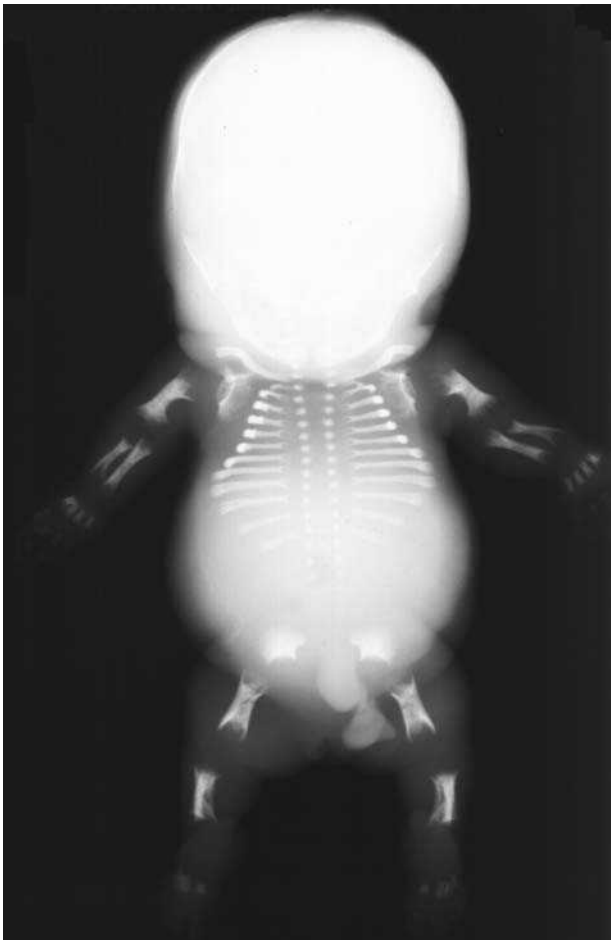
Polyhadramnios—A condition in which there is too much fluid around the fetus in the amniotic sac.

Differences in traits shared by all subtypes of achondrogenesis

Although all the subtypes of achondrogenesis share some characteristics, there are differences in some of these characteristics between subtypes. Type 1 achondrogenesis is generally considered to be more severe than type 2. This is supported by the shorter limbs found in type 1 and the lower average birth weight of type 1 infants compared to type 2 infants. Although any birth weight below 5.5 lbs (2,500 g) is considered to be low, type 1 infants average 2.6 lbs (1,200 g), whereas type 2 infants average 4.6 lbs (2,100 g). Additionally, both groups have a number of subtle skeletal abnormalities in addition to those already discussed.

Traits found in type 1 not shared by type 2 achondrogenesis

Type 1 achondrogenesis has two non-subtle characteristics that type 2 does not. Type 1 is often accompanied by abnormal connections either on the inside of the infant's heart or in the major blood vessels leading to and away from the heart. These defects are formally known as either atrial septal defects, ventral septal defects, or a **patent ductus arteriosus**. These connections allow oxygenated blood and deoxygenated blood to mix. Normally, oxygenated and deoxygenated blood are separated to ensure enough oxygen makes it to important tissues, like the brain. Mixing the blood results in less oxygen being



The x ray image of an infant with achondrogenesis shows the absence of spinal ossification as well as short bone formation throughout the body. *(Greenwood Genetic Center)*

pumped into the body and insufficient oxygenation of tissues around the body.

The other distinct type 1 characteristic is incomplete ossification. Ossification is the process of bone formation. In type 1A, incomplete ossification can be seen in many bones, including the skull. In type 1B, the skull is ossified, but bones other than the skull reveal incomplete ossification. No deficiency in ossification can be seen in type 2 achondrogenesis.

Diagnosis

Prenatal diagnosis of a skeletal disorder may be made by ultrasound. DNA testing may be used to determine the type of disorder, or to confirm the presence of a suspected disorder. Otherwise, diagnosis may be made by the physical appearance of the infant at birth, and/or x rays. DNA analysis or a microscopic examination of cartilage tissues may be used to identify the type of disorder.

Treatment and management

As of 2001, there is no treatment for the underlying disorder. Parents should consider mental health and **genetic counseling** to deal with the grief of losing a child, and to understand the risks of the disorder recurring in subsequent children. Support groups may be helpful in the pursuit of these goals. It is important for genetic counseling purposes to determine the type of achondrogenesis that affected the child, since different types of achondrogenesis carry very different prognoses for future children.

Prognosis

This disorder is fatal at birth or soon after. Type 1 is considered more severe, partly because infants with type 1 are more likely to be stillborn and generally succumb to the disorder earlier than infants with type 2 achondrogenesis.

Resources

ORGANIZATIONS

International Center for Skeletal Dysplasia. St. Joseph Hospital, 7620 York Road, Towson, MD 21204. (410) 337-1250.

International Skeletal Dysplasia Registry. Cedars-Sinai Medical Center. 444 S. San Vicente Boulevard, Suite 1001, Los Angeles, CA 90048. (310) 855-7488. priore@mailgate.csmc.edu.

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408. (806) 737-8186 or (888) LPA-2001. lpadatabase@juno.com. <http://www.lpaonline.org>.

Parents of Dwarfed Children. 2524 Colt Terrace, Silver Spring, MD 20902. (301) 649-3275.

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Michael V. Zuck, PhD

Achondroplasia

Definition

Achondroplasia is a common form of dwarfism or short stature due to an autosomal dominant mutation (a mutation on one of the first 22 "non-sex" chromosomes) that causes an individual to have short stature with disproportionately short arms and legs, a large head, and distinctive facial features, including a prominent forehead and a flattened midface.

Description

Achondroplasia is a genetic form of dwarfism due to a problem of bone growth and development. There are many causes for dwarfism, including hormone imbalances and metabolic problems. Achondroplasia belongs to a class of dwarfism referred to as a chrondrodystrophy or skeletal **dysplasia**. All skeletal dysplasias are the result of a problem with bone formation or growth. There are over 100 different types of skeletal dysplasia. Achondroplasia is the most common and accounts for half of all known skeletal dysplasias.

Achondroplasia is easily recognizable. Affected individuals have disproportionate short stature, large heads with characteristic facial features, and disproportionate shortening of their limbs. Most individuals with achondroplasia have a normal IQ. The motor development of infants is delayed due to hypotonia (low muscle tone) and their physical differences (large heads and small bones). The motor development of children with achondroplasia eventually catches up with that of their peers. Individuals with achondroplasia can have medical complications that range from mild to severe. Because of the differences in their bone structure, these individuals are prone to middle ear infections. They are also at risk for neurologic problems due to spinal cord compression. The spinal canal (which holds the spinal cord) is smaller than normal in achondroplasia. The American Academy of Pediatrics' Committee on Genetics has developed guidelines for the medical management of children with achondroplasia.

The short stature of achondroplasia can be a socially isolating and physically challenging. Most public places are not adapted to individuals of short stature and this can limit their activities. Children and adults with achondroplasia can be socially ostracized due to their physical appearance. Many people erroneously assume that individuals with achondroplasia have limited abilities. It is very important to increase awareness with educational programs and to take proactive steps to foster self-esteem in children with achondroplasia.

Genetic profile

Achondroplasia is caused by a mutation, or change, in the fibroblast growth factor receptor 3 **gene** (FGFR3) located on the short arm of chromosome 4.

Genes contain the instructions that tell a body how to form. They are composed of four different chemical bases–adenine (A), thymine (T), cytosine (C), and guanine (G). These bases are arranged like words in a sentence and the specific order of these four bases provide the instructions that a cell needs to form a protein.

FGFR (fibroblast growth factor receptor) genes provide the instruction for the formation of a cell receptor. Every cell in the body has an outer layer called a cell membrane that serves as a filter. Substances are transported into and out of the cells by receptors located on the surface of the cell membrane. Every cell has hundreds of different types of receptors. The fibroblast growth factor receptor transports fibroblast growth factors into a cell. Fibroblast growth factors play a role in the normal growth and development of bones. When the receptors for fibroblast growth factors do not work properly, the cell does not receive enough fibroblast growth factors and results in abnormal growth and development of bones.

Achondroplasia is caused by mutations in the FGFR3 gene. Two specific mutations account for approximately 99% of achondroplasia. The FGFR gene is comprised of 2,520 bases. In a normal (non-mutated) gene, base number 1138 is guanine (G). In most individuals with achondroplasia (98%), this guanine (G) has been replaced with adenine (A). In a small number of individuals with achondroplasia (1%), this guanine (G) has been replaced with cytosine (C). Both of these small substitutions cause a change in the fibroblast growth factor receptor (FGFR) that affects the function of this receptor.

Mutations in the FGFR3 gene are inherited in an autosomal dominant manner. Every individual has two FGFR3 genes—one from their father and one from their mother. In an autosomal dominant disorder, only one gene has to have a mutation for the person to have the disorder. Over 80% of individuals with achondroplasia are born to parents with average stature. Their achondroplasia is the result of a *de novo* or new mutation. No one knows the cause of *de novo* mutations or why they occur so frequently in achondroplasia. For reasons that are not yet understood, most new mutations occur in the FGFR3 gene that is inherited from the average-size father.

An individual with achondroplasia has a 50% chance of passing on their changed (mutated) gene to their children. An achondroplastic couple (both parents have achondroplasia) has a 25% chance that they will have a

KEY TERMS

Fibroblast growth factor receptor gene—A type of gene that codes for a cell membrane receptor involved in normal bone growth and development.

Rhizomelic—Disproportionate shortening of the upper part of a limb compared to the lower part of the limb.

child with average stature, a 50% chance that they will have a child with one achondroplasia gene (a heterozygote), and a 25% chance that a child will get two copies of the achondroplasia gene (a homozygote). Babies with homozygous achondroplasia are much more severely affected than babies with a single achondroplasia gene. These infants generally die very shortly after birth because of breathing problems caused by an extremely small chest.

Demographics

Because individuals with other forms of dwarfism are often misdiagnosed with achondroplasia, the exact incidence of achondroplasia is unknown. Estimates of the incidence of achondroplasia vary between 1/10,000 to 1/40,000 births. It is estimated that there are approximately 15,000 individuals with achondroplasia in the United States and 65,000 worldwide. Achondroplasia affects males and females in equal numbers.

Signs and symptoms

Individuals with achondroplasia have disproportionate short stature, large heads with characteristic facial features, and rhizomelic shortening of their limbs. Rhizomelic means "root limb." Rhizomelic shortening of the limbs means that those segments of a limb closest to the body (the root of the limb) are more severely affected. In individuals with achondroplasia, the upper arms are shorter than the forearms and the upper leg (thigh) is shorter than the lower leg.

In addition to shortened limbs, individuals with achondroplasia have other characteristic limb differences. People with achondroplasia have a limited ability to rotate and extend their elbows. They generally develop bowed legs and may have in-turned toes. Their hands and feet are short and broad, as are their fingers and toes. Their hands have been described as having a "trident" configuration. This term is based upon the trident fork used in Greek mythology and describes the unusual separation of their middle fingers. This unusual separation gives their hands a "three-pronged" appearance with the thumb and two small fingers on the side and the index and middle finger in the middle.

Individuals with achondroplasia have similar facial features and a large head (megalencephaly) due to the difference in the growth of the bones of the face and head. The exact reason for the increase in head size is not known, but it reflects increased brain size and can sometimes be due to **hydrocephalus**. People with achondroplasia have a protruding forehead (frontal bossing) and a relatively prominent chin. The prominent appearance of the chin is in part due to the relative flatness of their midface. While people with achondroplasia do resemble one another, they also resemble their family of origin.

Individuals with achondroplasia have shortening of their long bones. Women with achondroplasia have an average adult height of 48 in (122 cm). Men have an average adult height of 52 in (132 cm).

Diagnosis

Achondroplasia is generally diagnosed by physical examination at birth. The characteristic findings of short stature, rhizomelic shortening of the limbs, and specific facial features become more pronounced over time. In addition to being diagnosed by physical examination, individuals with achondroplasia have some specific bone changes that can be seen on an x ray. These include a smaller spinal canal and a small foramen magnum. The foramen magnum is the opening at the base of the skull. The spinal cord runs from the spinal canal through the foramen magnum and connects with the brain.

The diagnosis of achondroplasia can also be made prenatally either by ultrasound (sonogram) or by prenatal DNA testing. Sonograms use sound waves to provide an image of a fetus. The physical findings of achondroplasia (shortened long bones, trident hand) can be detected in the third trimester (last three months) of a pregnancy. Prior to the last three months of pregnancy, it is difficult to use a sonogram to diagnose achondroplasia because the physical features may not be obvious. Because of the large number of skeletal dysplasias, it can be very difficult to definitively diagnose achondroplasia by sonogram. Many other dwarfing syndromes can look very similar to achondroplasia on a sonogram.

Prenatal testing can also be done using DNA technology. A sample of tissue from a fetus is obtained by either chorionic villi sampling (CVS) or by **amniocentesis**. Chorionic villi sampling is generally done between 10-12 weeks of pregnancy and amniocentesis is done between 16-18 weeks of pregnancy. Chorionic villi sam-

pling involves removing a small amount of tissue from the developing placenta. The tissue in the placenta contains the same DNA as the fetus. Amniocentesis involves removing a small amount of fluid from around the fetus. This fluid contains some fetal skin cells. DNA can be isolated from these skin cells. The fetal DNA is then tested to determine if it contains either of the two mutations responsible for achondroplasia.

Prenatal DNA testing for achondroplasia is not routinely performed in low-risk pregnancies. This type of testing is generally limited to high-risk pregnancies, such as those in which both parents have achondroplasia. It is particularly helpful in determining if a fetus has received two abnormal genes (homozygous achondroplasia). This occurs when both parents have achondroplasia and each of them passes on their affected gene. The baby gets two copies of the achondroplasia gene. Babies with homozygous achondroplasia are much more severely affected than babies with heterozygous achondroplasia. Infants with homozygous achondroplasia generally die shortly after birth due to breathing problems caused by an extremely small chest.

DNA testing can also be performed on blood samples from children or adults. This is usually done if there is some doubt about the diagnosis of achondroplasia or in atypical cases.

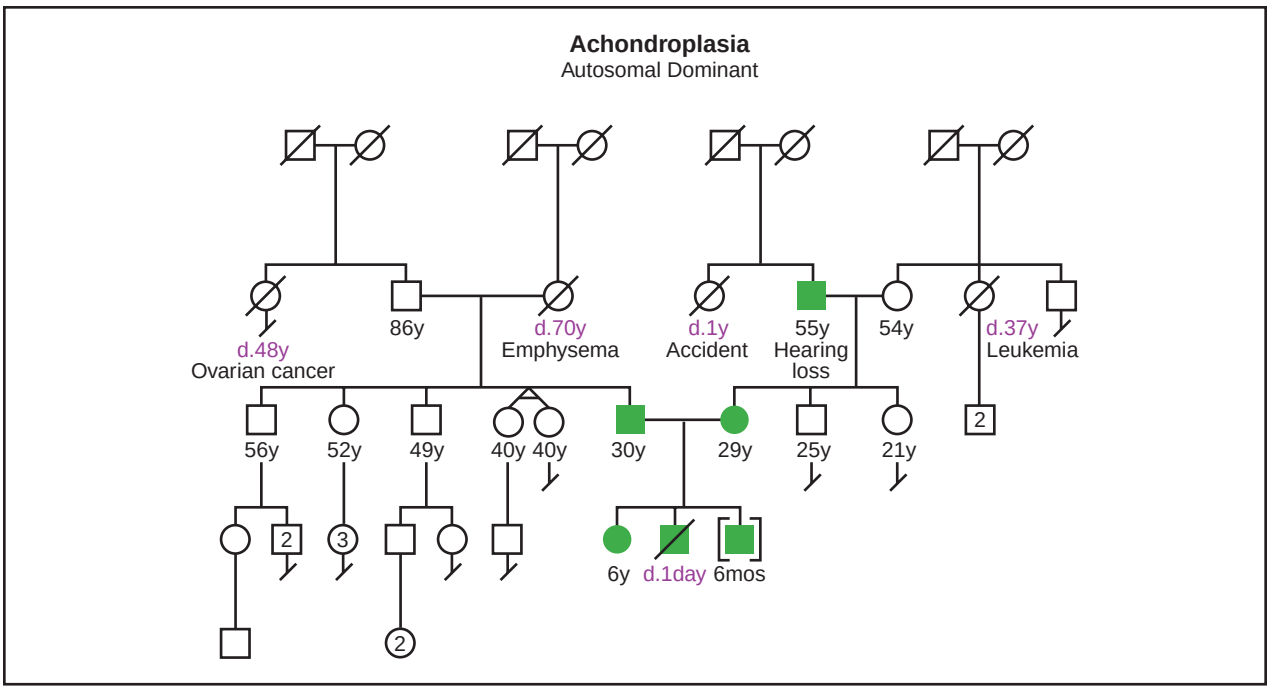
Treatment and management

There is no cure for achondroplasia. The recommendations for the medical management of individuals with achondroplasia have been outlined by the American Academy of Pediatrics' Committee on Genetics. The potential medical complications of achondroplasia range from mild (ear infections) to severe (spinal cord compression). By being aware of the potential medical complications and catching problems early, it may be possible to avert some of the long-term consequences of these complications. An individual with achondroplasia may have some, all, or none of these complications.

All children with achondroplasia should have their height, weight, and head circumference measured and plotted on growth curves specifically developed for children with achondroplasia. Measurements of head circumference are important to monitor for the development of hydrocephalus—a known but rare (<5%) complication of achondroplasia. Hydrocephalus (or water on the brain) is caused by an enlargement of the fluid-filled cavities of the brain (ventricles) due to a blockage that impedes the movement of the cerebrospinal fluid. Suspected hydrocephalus can be confirmed using imaging techniques such as a CT or MRI scan and can be treated with neurosurgery or shunting (draining) if it causes severe symptoms. Any child displaying neurologic problems such as lethargy, abnormal reflexes, or loss of muscle control should be seen by a neurologist to make sure they are not experiencing compression of their spinal cord. Compression of the spinal cord is common in individuals with achondroplasia because of the abnormal shape and small size of their foramen magnum (opening at the top of the spinal cord).

All children with achondroplasia should be monitored for sleep apnea, which occurs when an individual stops breathing during sleep. This can occur for several reasons, including obstruction of the throat by the tonsils and adenoids, spinal cord compression, and obesity. Individuals with achondroplasia are more prone to sleep apnea due to the changes in their spinal canal, foramen magnum, and because of their short necks. Treatment for sleep apnea depends on its cause. Obstructive sleep apnea is treated by surgically removing the tonsils and adenoids. Neurosurgery may be required to treat sleep apnea

This man has achondroplasia, a disorder characterized by short stature. *(Photo Researchers, Inc.)*



(Gale Group)

due to spinal cord compression. Weight management may also play a role in the treatment of sleep apnea.

Other potential problems in children with achondroplasia include overcrowding of the teeth (dental malocclusion), speech problems (articulation), and frequent ear infections (otitis media). Dental malocclusion (overcrowding of teeth) is treated with orthodontics. All children with achondroplasia should be evaluated by a speech therapist by two years of age because of possible problems with the development of clear speech (articulation). Articulation problems may be caused by orthodontic problems. Due to the abnormal shape of the eustachian tube in an individual with achondroplasia, they are very prone to ear infections (otitis media). Approximately 80% of infants with achondroplasia have an ear infection in the first year of life. About 78% of these infants require ventilation tubes to decrease the frequency of ear infections.

Weight management is extremely important for an individual with achondroplasia. Excess weight can exacerbate many of the potential orthopedic problems in an individual with achondroplasia such as bowed legs, curvature of the spine, and joint and lower back pain. Excess weight can also contribute to sleep apnea. Development of good eating habits and appropriate exercise programs should be encouraged in individuals with achondroplasia. These individuals should discuss their exercise programs with their health care provider. Because of the potential for spinal cord compression, care should be used in choosing appropriate forms of exercise.

The social adaptation of children with achondroplasia and their families should be closely monitored. Children with visible physical differences can have difficulties in school and socially. Support groups such as Little People of America can be a source of guidance on how to deal with these issues. It is important that children with achondroplasia not be limited in activities that pose no danger. In addition to monitoring their social adaptation, every effort should be made to physically adapt their surroundings for convenience and to improve independence. Physical adaptations can include stools to increase accessibility and lowering of switches and counters.

Two treatments have been used to try to increase the final adult height of individuals with achondroplasia –limb-lengthening and growth hormone therapy. There are risks and benefits to both treatments and as of 2001, they are still considered experimental.

Limb-lengthening involves surgically attaching external rods to the long bones in the arms and legs. These rods run parallel to the bone on the outside of the body. Over a period of 18-24 months, the tension on these rods is increased, which results in the lengthening of the underlying bone. This procedure is long, costly, and has potential complications such as pain, infections, and nerve problems. Limb-lengthening can increase overall height by 12-14 in (30.5-35.6 cm). It does not change the other physical manifestations of achondroplasia such as the appearance of the hands and face. This is an elective surgery and individuals must decide for them-

selves if it would be of benefit to them. The optimal age to perform this surgery is not known.

Growth hormone therapy has been used to treat some children with achondroplasia. Originally there was doubt about the effectiveness of this treatment because children with achondroplasia are not growth hormone deficient. However, studies have shown that rate of growth in children with achondroplasia treated with growth hormone does increase during the first two years of treatment. It is too early to say how effective this treatment is because the children involved in this study are still growing and have not reached their final adult height.

Prognosis

The prognosis for most people with achondroplasia is very good. In general, they have minimal medical problems, normal IQ, and most achieve success and have a long life regardless of their stature. The most serious medical barriers to an excellent prognosis are the neurologic complications that can arise in achondroplasia. Spinal cord compression is thought to increase the risk for SIDS to 7.5% in infants with achondroplasia and can lead to life-long complications such as paralysis if untreated. Obesity can increase the risk for heart disease and some studies have revealed an increased risk of unexplained death in the fourth and fifth decade of life.

Successful social adaptation plays an important role in the ultimate success and happiness of an individual with achondroplasia. It is very important that the career and life choices of an individual with achondroplasia not be limited by preconceived ideas about their abilities.

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ORGANIZATIONS

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408. (806) 737-8186 or (888) LPA-2001. lpadatabase@juno.com. <http://www.lpaonline.org>.

WEBSITES

The Human Growth Foundation. <http://www.hgfound.org/>

Little People of America: An Organization for People of Short Stature. <http://www.lpaonline.org/lpa.html>

Kathleen Fergus, MS

ACHOO syndrome

Definition

ACHOO syndrome is a generally benign condition characterized by sudden, uncontrollable sneezing after viewing a bright light.

Description

The ACHOO syndrome, standing for autosomal dominant compelling heliopthalmic outburst syndrome, is an inherited condition where a person will involuntarily sneeze after seeing a bright light. A person with this condition will sneeze multiple times, and in rare cases may sneeze 30-40 times. The syndrome is usually more intense if the person with the condition moves suddenly from darkness into an area with bright lights or sunlight.

Genetic profile

The ACHOO syndrome is thought to be inherited in an autosomal dominant pattern. This means that only one copy of the abnormal **gene** needs to be present for the syndrome to occur. If one parent has the condition, their children will have a 50% chance of also having the syndrome. One physician reported the condition in a family, where it was observed in the father and his brother, but not seen in the father's mother or his wife. Both the father and brother would sneeze twice when going from an area of darkness to an area of light. At four weeks of age, the father's daughter also started to sneeze whenever she was moved into bright sunlight.

Because of the relatively benign nature of the condition, there has been no reported scientific work trying to locate the gene responsible for the syndrome.

Demographics

Occurrence of the ACHOO syndrome is widespread in the general population. The few well-documented studies performed report the condition as being present in 23-33% of individuals. Men seem to be affected more than women. Studies on the occurrence of the syndrome in various ethnic groups are very limited. One study showed differences between whites and non-whites, while another study showed no difference.

Signs and symptoms

The prominent symptom of people with the ACHOO syndrome is sudden, involuntary sneezing when they see a bright light or sunlight. The way in which sneezing is

KEY TERMS

Allergy—Condition in which immune system is hypersensitive to contact with allergens; an abnormal response by the immune system to contact with an allergen; condition in which contact with allergen produces symptoms such as inflammation of tissues and production of excess mucus in respiratory system.

Antibody—A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

Antigen—A substance or organism that is foreign to the body and stimulates a response from the immune system.

Hypersensitivity—A process or reaction that occurs at above normal levels; overreaction to a stimulus.

Immune response—Defense mechanism of the body provided by its immune system in response to the presence of an antigen, such as the production of antibodies.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

triggered is not very well understood, but there are several theories that attempt to explain the syndrome.

One theory is that people who have the ACHOO syndrome have a hypersensitive reaction to light, just like some people have a sensitivity to cat hairs or pollen. When a person with the syndrome is exposed to a bright light, the same mechanism in the body that triggers a sneeze due to an irritant such as pollen somehow confuses light with that irritant and causes a sneeze to occur. Another idea is that the sneeze reflex in people with the ACHOO syndrome is somehow linked to real nasal allergies, although this does not explain the syndrome in people without nasal allergies. A third theory is that people with the ACHOO syndrome are very sensitive to seeing bright light. The sneeze reflex of the syndrome can then be thought of as an involuntary defense reaction against bright light; when the person sneezes, they automatically close their eyes.

Diagnosis

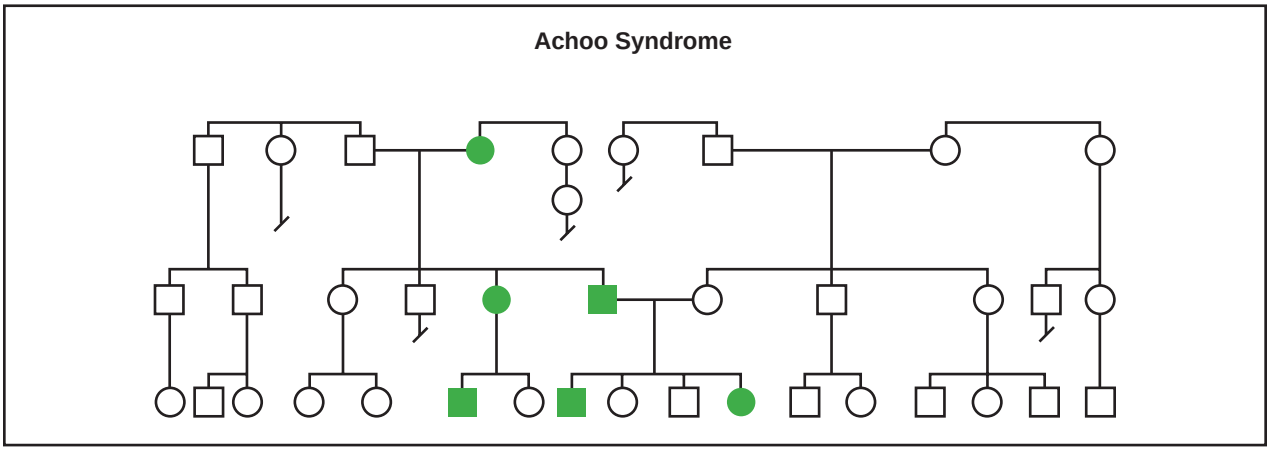
The ACHOO syndrome is diagnosed simply by observing the sneezing pattern of a person, and by looking into the sneezing patterns of the person's close relatives. If the person seems to sneeze every time they are exposed to a bright light, and if their parents and offspring do the same, then the diagnosis of the ACHOO syndrome can be made.

Currently, there are no known blood tests or other medical tests that can help diagnose the syndrome.

Treatment and management

There are no specific treatments for the ACHOO syndrome. Common measures, such as wearing sunglasses, can help people who are severely affected.

There have been reports that people who have nasal allergies have a higher incidence of the ACHOO syndrome. Therefore, it is sometimes assumed that medications that are used for allergies, such as antihistamines, could perhaps play a beneficial role in the ACHOO syn-



(Gale Group)

drome. However, no studies have successfully demonstrated that the syndrome is relieved by this type of medication. Alternative medicine, including homeopathy and herbal medicine, recommend a wide range of remedies for nasal allergies, these may accordingly also be helpful for the ACHOO syndrome.

Prognosis

People with the ACHOO syndrome generally have the condition for life. There is no evidence showing that the ACHOO syndrome in any way affects a person's life span.

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Edward R. Rosick, DO, MPH, MS

Acid maltase deficiency

Definition

Acid maltase deficiency, also called Pompe disease, is a non-sex linked recessive genetic disorder that is the most serious of the glycogen storage diseases affecting muscle tissue. It is one of several known congenital (present at birth) muscular diseases (myopathies), as distinct from a **muscular dystrophy**, which is a family of muscle disorders arising from faulty nutrition. The Dutch pathologist J. C. Pompe first described this genetic disorder in 1932.

Description

Acid maltase deficiency is also known as glycogen storage disease type II (GSD II) because it is characterized by a buildup of glycogen in the muscle cells. Glycogen is the chemical substance muscles use to store sugars and starches for later use. Some of the sugars and starches from the diet that are not immediately put to use are converted into glycogen and then stored in the muscle cells. These stores of glycogen are then broken down into sugars, as the muscles require them. Acid maltase is the chemical substance that regulates the amount of glycogen stored in muscle cells. When too much glycogen begins to accumulate in a muscle cell, acid maltase is released to break down this excess glycogen into products that will be either reabsorbed for later use in other cells or passed out of the body via the digestive system. Individuals affected with acid maltase deficiency have either a complete inability or a severely limited ability to produce acid maltase. Since these individuals cannot produce the amounts of acid maltase required to process excess glycogen in the muscle cells, the muscle cells become overrun with glycogen. This excess glycogen in the muscle cells causes a progressive degeneration of the muscle tissues.

Acid maltase is an enzyme. An enzyme is a chemical that facilitates (catalyzes) the chemical reaction of another chemical or of other chemicals; it is neither a reactant nor a product in the chemical reaction that it catalyzes. As a result, enzymes are not used up in chemical reactions, but rather recycled. One molecule of an enzyme may be used to catalyze the same chemical reaction over and over again several hundreds of thousands of times. All the enzymes necessary for catalyzing the various reactions of human life are produced within the body by genes. Genetic enzyme deficiency disorders, such as acid maltase deficiency, result from only one cause: the affected individual cannot produce enough of the necessary enzyme because the **gene** designed to make the enzyme is faulty. Enzymes are not used up in chemical reactions, but they do eventually wear out, or accidentally get expelled. Also, as an individual grows, they may require greater quantities of an enzyme. Therefore, most enzyme deficiency disorders will have a time component to them. Individuals with no ability to produce a particular enzyme may show effects of this deficiency at birth or shortly thereafter. Individuals with only a partial ability to produce a particular enzyme may not show the effects of this deficiency until their need for the enzyme, because of growth or maturation, has outpaced their ability to produce it.

The level of ability of individuals with acid maltase deficiency to produce acid maltase, or their ability to sustain existing levels of acid maltase, are the sole determinants of the severity of the observed symptoms in individuals and the age of onset of these symptoms.

Acid maltase deficiency is categorized into three separate types based on the age of onset of symptoms in the affected individual. Type a, or infantile, acid maltase deficiency usually begins to produce observable symptoms in affected individuals between the ages of two and five months. Type b, or childhood, acid maltase defi-

ciency usually begins to produce observable symptoms in affected individuals in early childhood. This type generally progresses much more slowly than infantile acid maltase deficiency. Type c, or adult, acid maltase deficiency generally begins to produce observable symptoms in affected individuals in the third or fourth decades of life. This type progresses even more slowly than childhood acid maltase deficiency.

Genetic profile

The locus of the gene responsible for acid maltase deficiency has been localized to 17q23. The severity of the associated symptoms and the age of onset in affected individuals have been closely tied to the particular mutation at this locus. Three specific mutations and one additional mutation type have been demonstrated to occur along the gene responsible for acid maltase deficiency. Each of these is associated with varying symptoms.

A gene is a particular segment of a particular chromosome. However, within the segment containing a particular gene there are two types of areas: introns and exons. Introns are sections of the segment that do not actively participate in the functioning of the gene. Exons are those sections that do actively participate in gene function. A typical gene consists of several areas that are exons divided by several areas of introns.

One mutation on the gene responsible for the production of acid maltase is a deletion of exon 18. A second mutation on the gene responsible for the production of acid maltase is the deletion of a single base pair of exon 2. Both these mutations are associated with a complete inability of the affected individual to produce acid maltase. Individuals with these mutations will invariably be affected with infantile (type a) acid maltase deficiency.

The third mutation on the gene responsible for the production of acid maltase is a complicated mutation within intron 1 that causes the cutting out of exon 2. This mutation is generally not complete in every copy of the gene within a given individual so it is associated with a partial ability of the affected individual to produce acid maltase. Individuals with this mutation will be affected with either childhood (type b), or, more commonly, adult (type c) acid maltase deficiency. In fact, greater than 70% of all individuals affected with adult acid maltase deficiency possess this particular mutation.

The final mutation class known to occur on the gene responsible for the production of acid maltase is missense at various locations along the various exons. Missense is the alteration of a single coding sequence (codon) that codes for a single amino acid that will be used to build the protein that is the precursor to the acid maltase molecule. These missense mutations generally prevent the production of acid maltase and lead to infantile (type a) acid maltase deficiency.

The exact mutations responsible for the other 30% of the adult (type c) and the remainder of the childhood (type b) acid maltase deficiency cases have not yet been determined.

Demographics

Acid maltase deficiency is observed in approximately 1 in every 100,000 live births. In 2000, it was estimated that between 5,000 and 10,000 people were living somewhere in the developed world with a diagnosed case of acid maltase deficiency. It is observed in equal numbers of males and females and across all ethnic subpopulations.

Since acid maltase deficiency is a recessive disorder, both parents must be carriers of the disorder for it to be passed to their children. In the case of carrier parents with one child affected by acid maltase deficiency, there is a 25% likelihood that their next child will also be affected with the disorder. However, because type c (adult) acid maltase deficiency generally does not show symptoms in the affected individual until that individual is past 30, it is possible for an affected individual to parent children. In this case, the probability of a second child being affected with acid maltase deficiency is 50%. Should two affected individuals bear offspring; the probability of their child being affected with acid maltase deficiency is 100%.

In families with more than one affected child, the symptoms of the siblings will closely correspond. That is, if one child develops infantile acid maltase deficiency, a second child, if affected with the disorder, will also develop the infantile form.

Signs and symptoms

The symptoms of acid maltase deficiency vary depending on the severity of the deficiency of acid maltase in the affected individual. The most acid maltase deficient individuals will develop infantile acid maltase deficiency and will exhibit the most severe symptoms. Likewise, the least acid maltase deficient individuals will develop adult acid maltase deficiency and have less severe symptoms.

Infantile (type a) acid maltase deficiency is characterized by the so-called “floppy baby” syndrome. This condition is caused by extreme weakness and lack of tone of the skeletal muscles. This observed weakness in the skeletal muscles is accompanied by the much more serious problems of overall weakness of the heart muscle (cardiomyopathy) and the muscles of the respiratory sys-

tem, primarily the diaphragm. Enlargement of the heart (cardiomegaly), tongue, and liver are also observed. Glycogen accumulation is observed in most tissues of the body.

Childhood (type b) acid maltase deficiency is characterized by weakness of the muscles of the trunk and large muscle mass with little muscle tone. This is due to a buildup of glycogen in the muscle cells. The heart and liver of those affected with childhood maltase deficiency are generally normal. However, there is a progressive weakening of the skeletal and respiratory muscles. The observed muscle weakness in childhood acid maltase deficiency affected individuals gradually progresses from the muscles of the trunk to the muscles of the arms and the legs. Glycogen accumulation is observed primarily in the muscle tissues.

Adult (type c) acid maltase deficiency is characterized by fatigue in younger affected individuals and by weakness of the muscles of the trunk in older affected individuals. The observed muscle weakness in adult acid maltase deficiency affected individuals gradually progresses from the muscles of the trunk to the muscles of the arms and the legs. High blood pressure in the artery that delivers blood to the lungs (pulmonary hypertension) is also generally observed in affected adults. Glycogen accumulation is observed primarily in the muscle tissues.

Diagnosis

Infantile acid maltase deficiency is generally diagnosed between the ages of two and five months when symptoms begin to appear. The first indicator of infantile acid maltase deficiency is general weakness and lack of tone (hypotonia) of the skeletal muscles, particularly those of the trunk.

A blood test called a serum CK test is the most commonly used test to determine whether muscular degeneration is causing an observed muscular weakness. It is used to rule out other possible causes of muscle weakness, such as nerve problems. To determine the CK serum level, blood is drawn and separated into the part containing the cells and the liquid remaining (the serum). The serum is then tested for the amount of creatine kinase (CK) present. Creatine kinase is an enzyme found almost exclusively in the muscle cells and not typically in high amounts in the bloodstream. Higher than normal amounts of CK in the blood serum indicate that muscular degeneration is occurring: that the muscle cells are breaking open and spilling their contents, including the enzyme creatine kinase (CK) into the bloodstream. Individuals affected with acid maltase deficiency have extremely high serum CK levels. Those affected with infantile acid maltase deficiency have much higher serum CK levels than those affected with the childhood or adult forms. The actual serum CK level, once observed to be higher than normal, can also be used to differentiate between various types of muscular degeneration.

Serum CK levels cannot be used to distinguish acid maltase deficiency from other glycogen storage diseases.

KEY TERMS

Acid maltase—The enzyme that regulates the amount of glycogen stored in muscle cells. When too much glycogen is present, acid maltase is released to break it down into waste products.

Acidosis—A condition of decreased alkalinity resulting from abnormally high acid levels (low pH) in the blood and tissues. Usually indicated by sickly sweet breath, headaches, nausea, vomiting, and visual impairments.

Catalyze—Facilitate. A catalyst lowers the amount of energy required for a specific chemical reaction to occur. Catalysts are not used up in the chemical reactions they facilitate.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Exon—The expressed portion of a gene. The exons of genes are those portions that actually chemically code for the protein or polypeptide that the gene is responsible for producing.

Fibroblast—Cells that form connective tissue fibers like skin.

Glycogen—The chemical substance used by muscles to store sugars and starches for later use. It is composed of repeating units of glucose.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Intron—That portion of the DNA sequence of a gene that is not directly involved in the formation of the chemical that the gene codes for.

Myopathy—Any abnormal condition or disease of the muscle.

Serum CK test—A blood test that determines the amount of the enzyme creatine kinase (CK) in the blood serum. An elevated level of CK in the blood indicates that muscular degeneration has occurred and/or is occurring.

Acid maltase deficiency (type II glycogen storage disease) is differentially diagnosed from type I glycogen storage disease by blood tests for abnormally low levels of glucose (hypoglycemia) and a low pH, or high acidity, (acidosis). Hypoglycemia and acidosis are both characteristic of type I glycogen storage disease, but neither is characteristic of acid maltase deficiency.

It is sometimes possible to determine the abnormally low levels of the acid maltase enzyme in the white blood cells (leukocytes) removed during the above blood serum tests. If these levels can be determined and they are abnormally low, a definitive diagnosis of acid maltase deficiency can be made. When the results of this leukocyte test are not clear, acid maltase deficiency types a and b may be positively diagnosed by testing muscles cells removed from the affected individual (muscle biopsy) for the actual absence or lack of sufficient acid maltase. This test is 100% accurate for type a and type b acid maltase deficiency, but it may give improper results for type c acid maltase deficiency. In these hard-to-identify cases of type c acid maltase deficiency, an identical test to that performed on the leukocytes may be performed on cultured fibroblasts grown from a sample from the affected individual. This test is 100% accurate for type c acid maltase deficiency.

Treatment and management

As of early 2001, there is no treatment or cure for acid maltase deficiency. The only potential treatment for this deficiency is enzyme replacement therapy. This approach was initially undertaken in the 1970s for acid maltase deficiency with no success. A new enzyme replacement therapy is, however, currently in human clinical trials that began in 1999.

Prognosis

Acid maltase deficiency of all three types is 100% fatal. Individuals affected with infantile acid maltase deficiency generally die from heart or respiratory failure prior to age one. Individuals affected with childhood acid maltase deficiency generally die from respiratory failure between the ages of three and 24. Individuals affected with adult acid maltase deficiency generally die from respiratory failure within 10 to 20 years of the onset of symptoms.

Human clinical trials involving enzyme replacement therapy, in which a synthetic form of acid maltase is administered to affected individuals, were begun in 1999 at Duke University Medical Center in North Carolina and Erasmus University Rotterdam in the Netherlands. Genzyme Corporation and Pharming Group N. V. announced the first results of these trials in a joint press release on October 5, 2000. These two companies currently own the worldwide patent rights to the synthetic enzyme being studied. As of early 2001, these clinical trials are still in phase I/II of the three-stage testing process for use in humans.

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Acid Maltase Deficiency Association (AMDA). PO Box 700248, San Antonio, TX 78270-0248. (210) 494-6144 or (210) 490-7161. Fax: (210) 490-7161 or 210-497-3810. <http://www.amda-pompe.org>.

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Paul A. Johnson

Acrocallosal syndrome

Definition

Acrocallosal syndrome is a rare congenital disorder in which the individual has absence or only partial formation of the corpus callosum. This is accompanied by skull and facial malformations, and some degree of finger or toe malformations. Individuals may display motor and mental retardation. The cause of this genetic disorder is unknown, and the severity of the symptoms vary by individual.

Description

Acrocallosal syndrome was first described by Schinzel in 1979, and also may be referred to as Schinzel acrocallosal syndrome. The term acrocallosal refers to the involvement of the acra (fingers and toes) and the corpus callosum, the thick band of fibers joining the hemispheres of the brain. Reported in both males and females, the cause of the disorder is unknown. The major characteristic of the syndrome is the incomplete formation (hypoplasia) or absence (agenesis) of the corpus callosum. Facial appearance is typically similar among affected people. This includes a prominent forehead, an abnormal increase in the distance between the eyes (hypertelorism), and a large head (macrocephaly). Individuals have a degree of webbing or fusion (syndactyly), or duplication (polydactyly) of the fingers and toes. Occasionally, those affected may have a short upper lip, cleft palate, cysts that occur within the cranium (intracranial), hernias, or may develop seizure disorders. Less frequently, affected children have **congenital heart defects**, internal organ (visceral) or kidney (renal) abnormalities.

Moderate to severe mental retardation is reported with acrocallosal syndrome. Individuals usually display some form of poor muscle tone (hypotonia), and there may be a delay or absence of motor activities, walking, and talking. There is great variation of functioning and symptoms with this disorder, ranging from normal development to severe mental and motor retardation.

KEY TERMS

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Consanguinity—A mating between two people who are related to one another by blood.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Hypertelorism—A wider-than-normal space between the eyes.

Hypotonia—Reduced or diminished muscle tone.

Polydactyly—The presence of extra fingers or toes.

Syndactyly—Webbing or fusion between the fingers or toes.

Genetic profile

The cause of acrocallosal syndrome is unknown. There are sporadic, or random, cases, and reports of multiple cases within families. Studies involving affected families have suggested an autosomal recessive pattern of **inheritance**. This means that both parents carry the altered form of the **gene** and the affected child inherited both copies. Following this pattern, each child born will have a 25% risk of being affected.

To help determine which chromosome or gene location causes the syndrome, acrocallosal syndrome has been compared with similar disorders. One condition that presents similar symptoms and has a known genetic cause is **Greig cephalopolysyndactyly syndrome**. However, there is no genetic similarity between the two conditions. To date, no specific genetic cause for acrocallosal syndrome is known, and the disorder can only be identified by clinical symptoms.

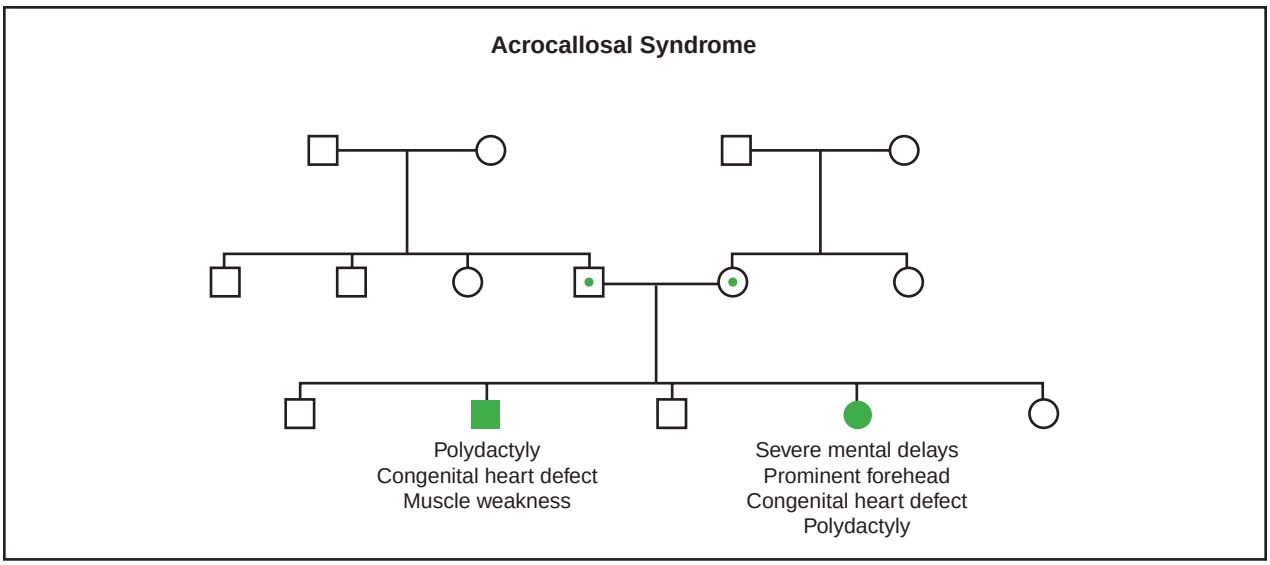
Demographics

Acrocallosal syndrome is extremely rare. Reports of this disorder may occur within family lines, or randomly. It affects both males and females. There are some reports of webbing of the fingers or toes (syndactyly) and relatedness (consanguinity) of the parents of affected children. However, affected children may also have unrelated, healthy parents and unaffected siblings.

Signs and symptoms

At birth, those with acrocallosal syndrome present the characteristic pattern of facial and limb malformations. Limb appearance ranges from minor webbing between the fingers or toes to near duplication of the hands or feet. Forehead prominence, increased distance between the eyes, and an enlarged head are the main features of facial appearance. X ray tests will reveal the absence or incomplete formation of the corpus callosum and the presence of any cysts within the cranium. The infant will usually display reduced muscle tone (hypotonia). This may lead to a drooling condition or feeding difficulties. Hypotonia can also contribute to a delay in growth and motor skills. Severe hypotonia is usually associated with a form of mental retardation.

Progress and functioning during the first year of life is dependent upon the severity of the symptoms. There has been a wide range of individual variation reported, and the degree to which symptoms affect each child may differ. Some children develop normally and will walk and talk within normal age limits, while others may experience a delay or absence of certain motor activities. Mental retardation may be moderate or severe. Some



(Gale Group)

children may develop seizure disorders. The degree and progression of mental retardation also varies by individual.

Diagnosis

The diagnosis of acrocallosal syndrome is based initially on the distinct pattern of facial and limb malformations. Computed tomography (CT), or a similar radiographic procedure of the head reveals the absence of the corpus callosum. Hand and foot x rays can be taken to confirm finger or toe abnormalities, and will determine the extent of fusion, webbing, or duplication of the digits (fingers or toes).

Prenatal diagnosis may not be possible due to the variability of the condition. However, prenatal ultrasound can detect duplication of the digits (polydactyly) and cerebral malformations. This may be especially informative for a woman who already has an affected child and has a 25% risk of having another affected child.

Treatment and management

Beginning in infancy, physical therapy may assist in the development of motor skills and muscle tone. Surgery to remove extra fingers and release fused fingers may improve movement and grasp, though the muscle tone may remain poor. Surgery to separate or remove affected toes may assist in walking and the comfort of footwear. Anti-epileptic therapy should be considered if a seizure disorder develops. Special education may be required, depending on the level of mental impairment.

Prognosis

At present, there are no preventative measures for acrocallosal syndrome, and the severity of symptoms and outcomes varies by individual. It has been found that the lifestyle of an individual with acrocallosal syndrome is dependent upon the degree of mental retardation and reduced muscle tone, rather than the extent of facial and limb malformations.

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ORGANIZATIONS

Agenesis of the Corpus Callosum (ACC) Network. Merrill Hall, University of Maine, Room 18, 5749, Orono, ME 04469-5749. (207) 581-3119. um-acc@maine.edu.

WEBSITES

AboutFace U.S.A. <http://www.aboutface2000.org>.
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Maureen Teresa Mahon, BSc, MFS

Acrocephalopolysyndactyly type II *see* **Carpenter syndrome**

Acrocephalosyndactyly type I *see* **Apert syndrome**

Acrocephalosyndactyly type III *see* **Saethre-Chotzen syndrome**

Acromatopsia *see* **Color blindness**

Acromegaly

Definition

Acromegaly is a rare condition caused by abnormally high amounts of human growth hormone (HGH). An organ in the brain known as the pituitary gland, normally secretes this growth hormone. Normal amounts of HGH are needed for normal growth and physical maturity in children. However, in acromegaly, there is an increased amount of HGH released, generally by a tumor that forms in the pituitary. Untreated, acromegaly can lead to numerous disabling conditions, as well as a significantly decreased life span.

Description

Acromegaly was first described in scientific detail by the French physician, Pierre Marie. In 1886, Dr. Marie, along with his assistant, Souza-Leite, described in detail 48 patients with acromegaly. These patients all exhibited a rapid growth in their height; significantly enlarged hands and feet; change in appearance of their faces; frequent headaches; and a high incidence of visual problems. Dr. Marie believed all of these problems were due to a defect in the patients' pituitary gland, a small glandular structure located in the middle of the brain.

While Dr. Marie was the first to formally state that a problem in the pituitary gland was responsible for the condition of acromegaly, the link between pituitary defects and acromegaly remained controversial for many years. It was not until 1909, when Dr. Harvey Cushing introduced the concepts of hyperpituitarism in reference to acromegaly, that the association became generally accepted. Dr. Cushing believed acromegaly was due to the pituitary gland, a small structure located deep in the brain and known to be somehow involved in growth, over-secreting some type of substance that caused patients to become "giants." Dr. Cushing also put forth the idea that the over-activity of the pituitary gland was caused by a tumor in the gland, an idea that was proven by autopsies done on patients with acromegaly. At the time, however, it still was not clear how a tumor in the pituitary gland could cause such changes in people afflicted with the tumor.

In the decades after World War II, the structure and function of the pituitary gland was further studied. Dr. Herbert Evans at the University of California at Berkley was the first to isolate many secretions, also known as hormones, which were found to be made in and secreted from the pituitary gland. One of these hormones was found to be human growth hormone, or HGH. It was also discovered that certain tumors can form in the pituitary gland and secrete high levels of HGH, resulting in abnormal growth and, as time progresses, acromegaly.

Acromegaly is a rare condition, with only about 1,000 cases per year in the United States among a total population of 250 million. Its striking consequence of excessive height has caused it to remain a fascinating disease among both scientists, doctors, and the public. Besides causing great height and unusual facial features, it is now known that acromegaly also causes serious conditions that can be life threatening, such as heart disease, respiratory disease, arthritis, neuromuscular problems, and diabetes. With early detection and treatment, the consequences of acromegaly can be minimized and patients afflicted with the condition can lead mainly healthy, productive lives.

Genetic profile

The genetics behind the majority of cases of acromegaly is still poorly understood. The most common cause of acromegaly is a benign (non-cancerous) tumor in the pituitary gland that secretes HGH. It is known that the benign tumor arises from cells in the pituitary gland, possibly due to a defect in the pituitary gland itself. The **gene** responsible for this tumor formation is unknown.

Even though the genetics of tumor formation in the pituitary gland leading to most cases of acromegaly is not yet known, there are other conditions that lead to acromegaly in which the genetic causes of the conditions are known. In a very rare condition, called familial acromegaly, there is a gene on chromosome 11 believed to cause the formation and growth of an HGH-secreting tumor in the pituitary gland. Familial acromegaly is transmitted in an autosomal dominant pattern—which

KEY TERMS

Dopamine—A neurochemical made in the brain that is involved in many brain activities, including movement and emotion.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Somatostatin—A body chemical, known as a cyclic peptide, involved in the release of human growth hormone from the pituitary gland.

means that it has an equal chance of affecting both boys and girls in a single family. This condition can also cause tumors in other areas of the body besides the pituitary, including the parathyroid gland, which controls the amount of calcium in the bloodstream, and the pancreas, which regulates insulin needed for the body to process sugars.

Another uncommon condition causing HGH-secreting tumors in the pituitary gland is called multiple endocrine neoplasia-1, or MEN-1. This is an autosomal dominant condition characterized by a combination of pituitary, parathyroid, and pancreatic tumors. The gene for this condition has also been found on chromosome 11 and is known as the MEN-1 gene. About half the patients with this abnormal gene will eventually develop acromegaly.

Carney syndrome is a rare autosomal dominant disorder that can cause HGH-secreting pituitary tumors and acromegaly in about 20% of patients who have the syndrome. Carney syndrome is associated with a defective gene on chromosome 2. Besides acromegaly, people with Carney syndrome also frequently have abnormal skin pigmentation, heart tumors, and tumors of the testicles and adrenal glands.

McCune-Albright syndrome is a very rare disorder that can cause acromegaly through HGH-secreting tumors in the pituitary. Other conditions associated with this syndrome are polycystic fibrous dysplasia (affecting bone growth, especially in the pelvis and long bones of the arms and legs), abnormal skin pigmentation, early puberty, and thyroid problems. The gene for the syndrome, named GNAS1, is located on chromosome 20.

Demographics

Acromegaly is a very rare condition. It is estimated to occur in about 30-60 individuals per million people. Both males and females seem to be affected equally. There also does not seem to be any difference in secondary complications of acromegaly between males and females. The condition has been recorded at all ages of life, from early childhood into old age. The frequency of chronic complications increases with age in both men and women.

Most cases of acromegaly are detected on an initial visit to a family physician, although some early or mild cases may be missed, causing a delay in the diagnosis. Some patients with acromegaly are initially diagnosed in specialty clinics, such as cardiology clinics and diabetic clinics when they present with secondary problems caused by the condition.

There is very little data on the differences of the occurrence of acromegaly among various ethnic and racial lines. The few studies that have been done show no real difference among racial or ethnic groups, with acromegaly showing up equally in Caucasians, African-Americans, and Asian-Americans.

Signs and symptoms

The signs and symptoms of acromegaly can range from striking to almost unseen. The most visible signs of the condition are greatly increased height and coarse facial features. People with acromegaly who have not received treatment early in the course of their condition have grown to be well over seven feet tall. Almost always with this spurt in height there is coarsening of facial features due to abnormal growth of the facial bones. Another very noticeable feature is enlargement of both the hands and feet, which, like the abnormal facial features, is the product of hormones and results in increased bone growth.

Other, less visible signs of acromegaly are increased sweating, constant and at times debilitating headaches, visual disturbances, and increase in hair growth. Loss of sexual desire is often seen in both men and women. Amenorrhea, the stopping of menstruation, is often a secondary condition associated with acromegaly in women.

There are further secondary complications of acromegaly that are not visible but can be life threatening. People with acromegaly are at greater risk for developing high blood pressure, cardiac disease, high cholesterol levels, arthritis and other degenerative diseases of the joints and spine, and diabetes. Acromegly also increases the risk of other tumors, some of them cancerous, in other areas of the body, especially the breast, colon, and to a lesser degree, prostate.

With adequate treatment, especially early in the course of the condition, many of the secondary symp-

toms of acromegaly can be halted or even reversed. Less life-threatening complications, such as headaches, visual problems, and increased sweating can be almost eliminated after adequate and timely treatment. More serious conditions such as heart disease, high blood pressure, and diabetes can be brought under control with treatment, although many times not totally eliminated.

Diagnosis

For most forms of acromegaly, there are no genetic tests yet available to diagnosis the condition in newborns or before birth. Diagnosis is made by recognizing the clinical signs and symptoms previously described. In certain very rare conditions such as multiple endocrine neoplasia-1 and Carney syndrome, the genetics of the conditions are known and can theoretically be tested for. However, the conditions are so seldom encountered that unless a family member has the condition, **genetic testing** is usually not done until clinical signs and symptoms are apparent.

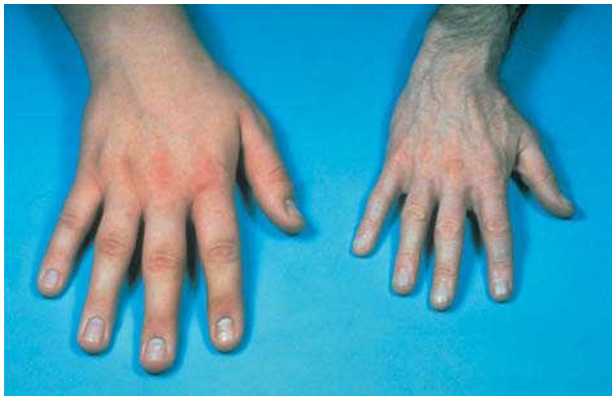
Treatment and management

The treatment and management of acromegaly has evolved over the past one hundred years from crude surgery to genetically engineered medications. Today, through precise surgery and medications, a large percentage of patients with acromegaly can have their symptoms brought under control, and in some cases totally cured.

The goal of all therapies, be it surgery or medications, is a reduction in the level of HGH to levels seen in people without acromegaly. This goal can be achieved either through the removal or destruction of the tumor secreting the hormone, inhibition of HGH from the tumor, or blocking the effects of increased HGH on organs and other body systems outside the pituitary.

Surgical removal of the pituitary tumor is still the first treatment of choice for acromegaly. The rate at which a cure is achieved is determined by several factors, including the size of the tumor, whether or not it has spread outside the pituitary, and the level of HGH before the surgery. In patients with small tumors confined to the pituitary and exhibiting only moderately high HGH levels, the cure rate can be as high as 80–90%. In patients with larger tumors, especially those extending out of the pituitary, cure rates with surgery can be reduced to 40–60%.

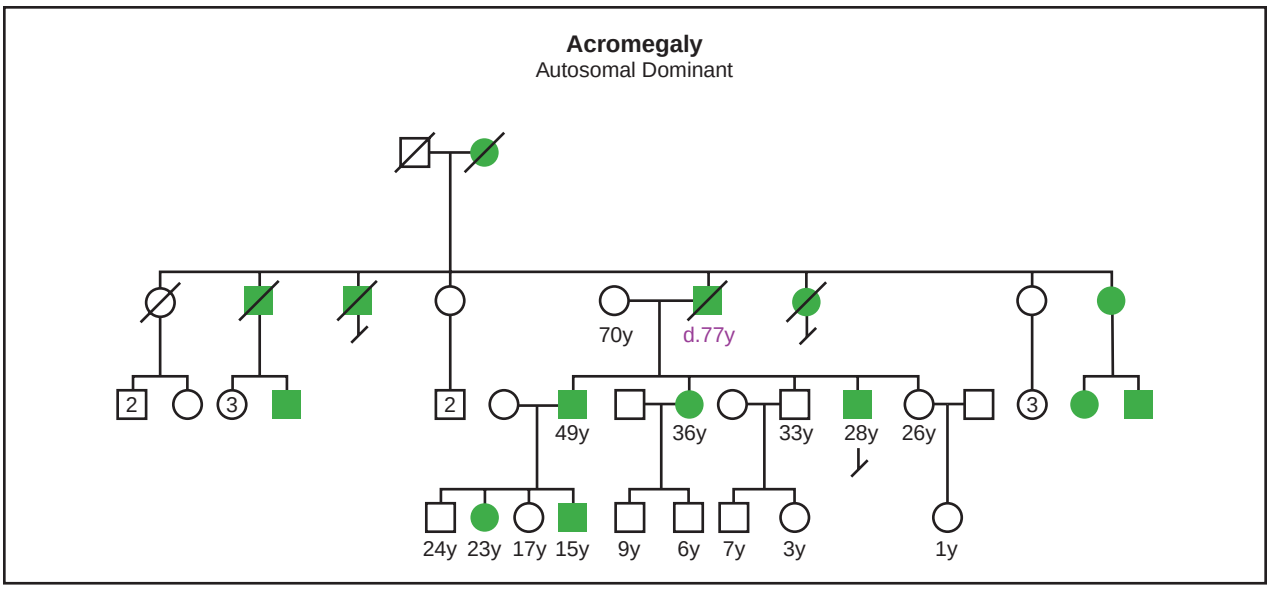
Radiation therapy is often a second line choice of treatment for acromegaly, especially in patients who have not achieved a cure with surgery. The treatment of acromegaly with radiation was used early on in the history of the condition, with the first report being written in 1909. Careful application of radiation can significantly reduce the size of pituitary tumors, subsequently decreasing high HGH levels. However, this decrease is often very slow, and it can take over ten years for the HGH levels to drop to normal. Treatment with radiation can also have significant side effects, including damage to the pituitary gland itself, visual loss, and brain damage. Some studies have also suggested that treatment with radiation can lead to tumor formation in other areas of the brain.



Comparison of hand size between a patient with acromegaly (left) and that of an unaffected adult (right). *(Custom Medical Stock Photo, Inc.)*

The use of medications in the treatment of acromegaly has gained importance over the past few decades in the treatment of the condition. Medications available today include Bromocriptine, octreotide and lanreotide, and a genetically engineered HGH receptor antagonist known as Pegvisomant. All of these medications are generally used in combination with surgery or radiation, although there is debate whether or not the medications could or should be used as first-line agents.

Bromocriptine is known as a dopamine agonist, and was one of the first pharmaceutical agents to be used to lower HGH levels in acromegaly. However, bromocriptine is not effective in a majority of cases, and the medications octreotide and lanreotide have supplemented its use. These medications are also known as somatostatin analogues. They decrease both the size of HGH-secreting pituitary tumors and the secretion of HGH itself. In multiple studies, they have been shown to normalize HGH levels in about 50% of cases and show significant tumor shrinkage in 45% of cases. The drawbacks to using both octreotide and lanreotide include multiple weekly dosing over a 12-month period, as well as acute side effects such as nausea, stomach pain, and diarrhea. Also, long term use of these medications results in an increased risk of developing gallstones.



(Gale Group)

Pegvisomant is a unique, recently developed genetically engineered HGH receptor antagonist. This medication does not decrease the amount of HGH secreted from pituitary tumors; rather, it desensitizes other organs of the body to the effects of the increased HGH circulating in the body. In medical trials, Pegvisomant was well tolerated and resulted in significant symptomatic improvement. It is hoped that with a combination of surgery to decrease the tumor size and the use of a HGH antagonist like Pegvisomant, both the acute and chronic debilitating symptoms of acromegaly can be greatly diminished, if not totally eliminated.

Prognosis

The prognosis for patients with acromegaly who receive prompt treatment is good, although there are still complications. Patients who do not receive treatment, or those who receive it late in the course of the condition, have frequent and debilitating secondary complications as well as a greater chance for early death.

There are only a few reliable studies examining the overall health benefits of treatment versus no treatment for patients with acromegaly. One study showed that those receiving treatment before the age of 40 years had a much better chance of not developing serious complications then those who were treated after 40 years of age. Those receiving earlier treatment had less chance of developing heart disease, high blood pressure, and diabetes, as well as other secondary complications of the condition.

Even with treatment, mortality rates for people with acromegaly are increased when compared to the rest of the population. The principal causes of early death are cardiac disease, strokes, **cancer**, and respiratory failure. The level of HGH after treatment appears to offer the best statistics for predicting early mortality, with higher levels of post-treatment HGH corresponding to a greater, earlier mortality risk.

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Edward R Rosick, DO, MPH, MS

Adams-Oliver syndrome

Definition

Adams-Oliver syndrome (AOS) is a condition involving the combination of congenital scalp defects (called aplasia cutis congenita) and a specific type of limb defect.

Description

Adams-Oliver syndrome is a genetic condition characterized by aplasia cutis congenita, most commonly of the scalp and skull, and terminal transverse limb defects. Congenital heart disease has also been reported in individuals with this condition. The exact cause of the condition is not well-understood. There is extreme variability in the severity of problems between families with AOS.

Genetic profile

There have been both familial and non-familial cases of Adams-Oliver syndrome reported. The majority of genetic cases have been inherited in an autosomal dominant manner, but autosomal recessive and sporadic **inheritance** have also been reported. A difference in the presentation of AOS in the dominant versus recessive form has not been documented.

Autosomal dominant inheritance means that only one abnormal **gene** copy is required for the disease to occur. For persons with a copy of the gene, the risk of passing it to their offspring is one in two or 50%.

Autosomal recessive inheritance means that two defective gene copies must be inherited, one from each parent, for the disease to manifest itself. Persons with only one **gene mutation** are carriers for the disorder. Individuals who are a carrier for the recessive type of Adams-Oliver syndrome do not have any symptoms (asymptomatic) and do not know they are a carrier unless they have had a child with the syndrome. Carrier testing is not available since the gene location is not known at this time. The liklihood that each member of a couple would be a carrier for a mutation in the same gene is higher in people who are related (called consanguineous). When both parents are carriers for the recessive type of Adams-Oliver syndrome, there is a one in four chance (25%) in each pregnancy for a child to have the disease. There is a two in three chance that a healthy sibling of an affected child is a carrier.

Sporadic occurrences of AOS may be caused by a dominant gene with variable expressivity (no one else in the family has symptoms, but some are actually gene carriers), a new (dominant) mutation occuring during the formation of the embryo where neither parent is a carrier, or the existence of both genetic and non-genetic causes for the same syndrome.

Different mechanisms have been postulated to explain how Adams-Oliver syndrome occurs. They include trauma, uterine compression, amniotic band sequence (a condition resulting from strands of the amnion membrane causing amputation of parts of the fetus), vascular disruption (blockage of blood flow to a developing part or parts of the fetus), and a large blood clot in the placenta which blocks certain important blood vessels and interrupts blood supply to developing structures. Recently, Adams-Oliver syndrome has been hypothesized to occur as a result of abnormalities in small vessel structures that occur very early in embryo formation. The vascular anomaly could be the result of a genetic defect causing decreased stability of embryonic blood vessels in the presence of specific forces.

Demographics

Adams-Oliver syndrome was first described in 1945. As of 2000, there have been over 125 cases reported in the medical literature. There does not appear to be any ethnic difference in prevalence of this condition.

Signs and symptoms

Limb defects are the most common occurrence in Adams-Oliver syndrome, affecting about 84% of patients. The type of limb defect is usually asymmetrical (not the same on both sides), with a tendency to involve both sides of the body (bilateral), more often the lower limbs than the upper limbs. There is a wide range of severity in the limb defects, from something minimal like small or missing finger or toenails (called nail hypoplasia), to the more severe absence of hands, feet, or lower legs. Other more moderate limb defects that have been reported include webbing (syndactyly) of the skin (cutaneous syndactyly) or bones (bony syndactyly) of the fingers or toes, claw-hand malformation (ectrodactly), and **brachydactyly** (shortened fingers or toes). Brachydactyly is the most common limb defect in AOS.

Congenital cutis aplasia is the second most common problem and is present in about 75% of patients with Adams-Oliver syndrome. In 64% of patients with congenital cutis aplasia, there is also an underlying scull defect. More rarely, scull defects can be seen without scalp defects and may be mistaken for an enlarged soft spot (fontanelle).

Congenital heart defects have been reported to occur in between 13–20% of patients with Adams-Oliver syndrome.

KEY TERMS

Aplasia cutis congenita (ACC)—A group of disorders with different causes whose common characteristic is absence of skin in a defined area.

Congenital—Refers to a disorder which is present at birth.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Incomplete penetrance—Individuals who inherited an abnormal gene for a disorder, but do not exhibit symptoms of that disorder.

Variable expression—Instances in which an identical genetic mutation leads to varying traits from affected individual to affected individual. This variance may occur between members of two separately affected families or it may occur between affected members of the same family.

Many different types of vascular (involving the blood vessels) and valvular (involving heart valves) problems have been reported in these patients.

Other clinical features seen with AOS, include short stature, kidney (renal) malformations, cleft palate, small eyes (micropthalmia), **spina bifida** occulta, extra (accessory) nipples, undescended testes, skin lesions, and neurological abnormalities. Mental retardation is present in a few cases.

Diagnosis

Aplasia cutis congenita is a physical finding that has many causes. To determine whether a patient has Adams-Oliver syndrome clinically, all individuals with aplasia cutis congenita should have a complete pregnancy and family history taken, as well as a complete medical evaluation. When possible, relevant family members should be examined for evidence of the condition. When aplasia cutis congenita is discovered at birth, the placenta should be evaluated. Physical exam of the affected infant includes evaluation of other related structures, specifically teeth, hair, and other areas of skin, nails, and central nervous system. Once this evaluation has been completed and a specific diagnosis of Adams-Oliver syndrome has been established or refuted, **genetic counseling** can be provided.

Prenatal diagnosis by ultrasound of the limb defects and possibly some other abnormalities associated with AOS is possible, but clinical confirmation of the diagnosis occurs after birth. Since the gene (or genes) causing AOS have not been isolated, prenatal diagnostic procedures such as **amniocentesis** or chorionic villus sampling are not indicated.

Treatment and management

The treatment for AOS is different for each individual and is tailored to the specific symptoms. If leg-length discrepancy is present, corrective shoes that increase the sole for the unaffected leg to prevent **scoliosis** and ambulation difficulties can be worn. Orthopedic devices such as prostheses are sometimes recommended. Patients should be referred to a physician specializing in treating patients with limb defects early in life. Surgery for congenital defects and skin grafting for scalp defects may be necessary (about 30% of patients required skin grafting in one study).

Special devices for writing or other activities may be necessary if hand malformations are present.

About 30% of patients in one study suffered major hemmorrhage from the scalp defect. Twenty percent of patients had local infection of the scalp defect. Treatment such as transfusion or antibiotic therapy may be required in these cases.

Appropriate special education services are necessary for those with mental retardation. Counseling and support related to limb defeciency issues are essential for coping. Support groups can provide valuable peer referrals and information.

Prognosis

AOS does not usually alter lifespan, although complications from associated abnormalities such as mental retardation can cause problems. About 5% of the scalp defects that hemorrhaged severly were fatal. Rare cases of meningitis as a result of infection of the scalp defect have been reported. Asymmetry of the limbs can interfere with their proper function and cause pain. Psychological issues relating to disfigurement are possible.

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ORGANIZATIONS

Cherub Association of Families & Friends of Limb Disorder Children. 8401 Powers Rd., Batavia, NY 14020. (716) 762-9997.

REACH—Association for Children with Hand or Arm Deficiency. 12 Wilson Way, Earl's Barton, Northamptonshire, United Kingdom, NN6 9NZ. 01 604 811041.

WEBSITES

OMIM—Online Mendelian inheritance in Man <http://www.ncbi.nlm.nig.gov>.

Amy Vance, MS, CGC

Addison disease *see* **Adrenoleukodystrophy (ALD)**

Adenomatous polyposis of the colon (APC) *see* **Familial adenomatous polyposis**

Adrenoleukodystrophy

Definition

Adrenoleukodystrophy is a progressive condition that affects the adrenal glands, the glands atop the kidneys responsible for the production of adrenalin, and myelin, which insulates the nerves in the brain and spinal cord.

Description

Adrenoleukodystrophy (ALD) was first described in the early 1900s and was originally called Schilder-Addision disease. It is named for the different parts of the body that are affected; "adreno" refers to the adrenal glands, "leuko" is the Greek word for white (myelin is often called the white matter in the brain and spinal cord), and "dystrophy" meaning impaired growth. Therefore, this disease affects the adrenal glands and the growth of the myelin in the brain and spinal cord. There is a wide range in the severity of symptoms. ALD mainly affects males, but occasionally females have mild or moderate symptoms.

Causes and effects

ALD is caused by problems in the peroxisomes. The peroxisomes are tiny structures in cells that help break down large molecules of fats into smaller ones so that they can be used by the body. In ALD the peroxisomes cannot break down a type of fat called very long chain fatty acids (VLCFA). There are two types of problems that occur because the VLCFA are not broken down. First, because the VLCFA cannot be broken down, they accumulate throughout the body, especially in the brain and the adrenal glands. Very high levels of VLCFA are also seen in the blood. The second type of problem occurs because the fats that are usually made when VLCFA are broken down are not produced. This is in part what happens in the adrenal glands and in the myelin.

The adrenal glands are located on top of each kidney in the abdomen. Part of the job of the adrenal glands is to use cholesterol (a type of fat made in the body when VLCFA are broken down) to make a few different steroids—chemical combinations that form the basis of hormones, body acids, and anabolic agents. The steroids are used to help the body properly use sodium and potassium and to break down proteins, carbohydrates, and other fats. Some of these steroids are also involved with sexual development and function.

The insulation that surrounds the nerves is called myelin and is also affected by the VLCFA not being broken down. Myelin is made up of a number of different proteins and fats. Normally the VLCFA break down and produce fats that make up part of the myelin. When the VLCFA cannot break down, the fats necessary to make the myelin are not made and the myelin is abnormal. In addition, for reasons not well understood, there is also active breakdown of myelin, also known as demyelination.

Genetic profile

ALD is caused by a mutation in a **gene** called the ALD gene. Genes contain the instructions for how the body grows and develops before and after a person is born. The ALD gene makes a protein called ALDP (ALD protein). Different proteins put together make the tissues and organs in the body such as myelin. ALDP is important because it helps VLCFA get into the peroxisomes. When there is a mutation in the ALD gene, the ALDP is abnormal or not present at all. As a result, the VCLFA cannot get into the peroxisomes and the VLCFA accumulate in other places in the body.

Genes are organized on structures called **chromosomes**. Hundreds to thousands of genes are found on each chromosome. There are 46 chromosomes in each cell of the body. These are grouped into 23 pairs. The first 22 pairs are the same in both males and females. The 23rd pair is called the sex chromosomes; having one X chromosome and one Y chromosome causes a person to be male; having two X chromosomes causes a person to be female. People get one member of each pair from the mother's egg and one member from the father's sperm.

The ALD gene is located on the X chromosome. Since males only have one X chromosome, they only have one copy of the ALD gene. Thus, when a male has a mutation in his ALD gene, he will have ALD. However, females have two X chromosomes and therefore have two copies of the ALD gene. If they have a mutation in one copy of their ALD genes, they may only have mild symptoms of ALD or no symptoms at all. This is because their normal copy of the ALD gene does make normal ALD protein. Females who have one copy of the ALD gene with a mutation and one normal copy are called carriers.

Inheritance

ALD is passed on through families by X-linked recessive **inheritance**. This means that affected males are related through females in the family and there are no males in the family that have passed ALD onto their sons. Females pass on one of their X chromosomes to their children—sons or daughters. For a female carrier, if her normal X chromosome is passed on, her son or daughter will be unaffected and cannot pass ALD onto their children. However, if the X chromosome with the ALD mutation is passed on, a daughter will be a carrier and the son would have ALD. Therefore, a female carrier has a 50% or one in two chance of having an unaffected child (son or daughter), a 25%, or one in four, chance of having a carrier daughter, and a 25% or one in four chance of having an affected son.

When males pass on an X chromosome, they have a daughter. When they pass on a Y chromosome, they have a son. Since the ALD mutation is on the X chromosome, an affected male will always pass the ALD mutation on to his daughters. However, when he has a son, he passes on the Y chromosome, and the son is not affected. Therefore, an affected male passes the ALD **gene mutation** on to all of his daughters, but none of his sons.

Demographics

ALD has been described in people from all different ethnic groups. Approximately one in 20,000 to one in 42,000 people have ALD.

Signs and symptoms

Adrenal insufficiency

Almost all individuals affected with ALD have problems with their adrenal glands not working properly. This is called adrenal insufficiency. These problems include sluggishness, weakness, weight loss, hypoglycemia, nausea, vomiting, darkening of the skin color, and mental changes. Because adrenal insufficiency can cause problems with regulating the balance of sodium and potassium in the body, a person can go into shock and a coma, which can be potentially life threatening. Since this aspect of ALD is readily treatable, it is important to identify these patients in order to prevent these complications.

Types of ALD

There is a wide range in the severity of symptoms and age of onset of ALD. All different severities have been seen within the same family. Therefore, a family who has many mildly affected members could still have a more severely affected member. ALD is roughly divided into three different types according to severity and age of onset. However, some patients do not fall neatly into one of these categories and instead fall somewhere in between. Each type is given a different name, although all have mutations (changes in the genetic code) in the same gene and the same type of inheritance.

The most severe form of ALD is called childhood ALD. About 35% of people with ALD have this type. These children usually have normal development in the first few years of life. Symptoms typically begin between four and eight years of age. Very rarely is the onset before the age of three or after the age of 15. In some boys, the first symptom may be seizures. In other children, they become hyperactive and have behavioral problems that may initially be diagnosed as attention deficit disorder. Early signs may also include poor school performance due to impaired vision that is not correctable by eyeglasses. Although these symptoms may last for a few months, other more severe problems develop. These include increasing problems with schoolwork and deterioration in handwriting and speech. They usually develop clumsiness, difficulty in reading and comprehension of written material, aggressive or uninhibited behavior, and various personality and behavioral changes. Most of these boys have problems with their adrenal glands by the time their first symptoms are noticed.

A milder form of ALD called adrenomyeloneuropathy (AMN) usually has a symptom onset at the age of 20 or later. Approximately 40–45% of people with ALD have this type. The first symptoms are typically a progressive stiffness and weakness in the legs. Problems with urination and sexual function may also develop. Symptoms slowly progress over many years. Less than 20% of men with AMN will develop significant brain involvement that leads to cognitive and behavioral problems that are severe and may cause a shortened life span. About 70% of men with AMN will have problems with their adrenal glands when other symptoms are first noticed.

A third type of ALD is called Addison disease and affects about 10% of all of those with ALD. In this condition, people do not have the neurologic symptoms associated with ALD and AMN, but do have problems

resulting from adrenal insufficiency. Symptoms typically begin between two years of age and adulthood. The first symptoms are often vomiting, weakness, or coma. People with Addision disease may or may not have darker skin. Many who are initially diagnosed with Addison disease will later develop symptoms of AMN.

In female carriers, about 20% will develop mild to moderate progressive stiffness and weakness in the legs and sometimes problems with urination. Rarely do they develop adrenal insufficiency. Symptoms in women generally do not begin before middle age.

Diagnosis

When the diagnosis of ALD is suspected, a test called magnetic resonance imaging (MRI) is usually required. In this test, pictures of the brain are taken and the amount of white matter (myelin) in the brain is measured. In people with symptoms of ALD, there are usually characteristic changes in the white matter. An MRI can be helpful in making the diagnosis of ALD, but if changes are seen on MRI, it does not confirm the diagnosis of ALD. Changes in the white matter may only be seen after 1–2 years of age when the brain has matured.

A definitive diagnosis of ALD can be made by measuring the level of the VLCFA in the blood. In 99.9% of males with all types of ALD, the level of the VLCFA in blood is very high. This is diagnostic of ALD.

When ALD is suspected, testing should also be performed to measure the adrenal function. In 90% of boys with symptoms of ALD and 70% of men with AMN, the adrenal glands are affected.

Approximately 85% of female carriers will have higher than normal levels of VLCFA in their blood. However, 15–20% of female carriers will have normal levels of VLCFA in their blood, which gives a "false negative" result. If a woman wants to be certain about her carrier status, **genetic testing** to look for a specific mutation in the ALD gene can be performed. This testing usually involves drawing a small amount of blood. Before a woman could have testing to determine her carrier status, a mutation in the ALD gene must have already been found in an affected member of the family. If a mutation in the ALD gene has already been found in another family member, testing on another child suspected on having ALD would be done to look at the mutation known to cause ALD in the family.

Treatment and management

When the diagnosis of ALD is made, an important first step is to measure the level of adrenal function. If there is adrenal insufficiency, treatment should be given by steroid replacement, which can prove to be life saving. Adrenal function should be tested periodically.

Early on, it was thought that reducing the VLCFA in a person's diet would help reduce the symptoms of ALD. Although some VLCFA does come from the diet, most of it is produced in the body. Therefore, altering the diet alone does not cure ALD.

Lorenzo's oil

In the early 1990s, a film called *Lorenzo's Oil* told an embellished account of a real life family who had a young son with ALD and their search to find a cure for him. A possible treatment was found and was named Lorenzo's oil, after their son, Lorenzo. The Lorenzo's oil therapy worked to reduce the level of VLCFA in the blood. The idea was that if the level of VLCFA could be reduced, perhaps it would cure or help the symptoms. After a number of years of use, Lorenzo's oil unfortunately does not seem to be an effective treatment, at least in those with advanced signs and symptoms. Although it does reduce the level of VLCFA in blood, it does not seem to alter a person's symptoms.

Bone marrow transplant

One promising treatment is bone marrow transplant. However, this is a potentially dangerous procedure that

KEY TERMS

Adrenal insufficiency—Problems with the adrenal glands that can be life threatening if not treated. Symptoms include sluggishness, weakness, weight loss, vomiting, darkening of the skin and mental changes.

Central nervous system (CNS)—In humans, the central nervous system is composed of the brain, the cranial nerves and the spinal cord. It is responsible for the coordination and control of all body activities.

Leukodystrophy—A disease that affects the white matter called myelin in the CNS.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system, which helps them conduct impulses more quickly.

Peroxisomes—Tiny structures in the cells that break down fats so that the body can use them.

Very long chain fatty acids (VLCFA)—A type of fat that is normally broken down by the peroxisomes into other fats that can be used by the body.

has a 10–20% rate of death. As of early 2001, information is available on a limited number of patients. In the very small number of patients who have had a bone marrow transplant, a few have had their condition stabilize and a few have even made slight improvements. However, all of these people had the bone marrow transplant at an early stage of their disease. This treatment does have drawbacks including the fact that there are limited numbers of donors who are a suitable "match" and a significant chance that complications will develop from the transplant. Early data suggests that bone marrow transplant is most effective when performed at an early stage of the disease when abnormalities are first seen through MRI. Additional long-term studies are necessary to determine the overall success of these procedures.

Other treatments

Research is being done with other treatments such as lovastatin and 4-phenylbutyrate, both of which may help lower VLCFA levels in cells, but more work is necessary to determine their effectiveness. **Gene therapy**, a possible method of treatment, works by replacing, changing, or supplementing non-working genes. Although different gene therapy methods are being testing on animals, they are not ready for human trials.

Other types of therapy and supportive care are of benefit to both affected boys and their families. Physical therapy can help reduce stiffness and occupational therapy can help make the home more accessible. Support from psychologists and other families who have been or are in a similar situation can be invaluable. Many men with AMN lead successful personal and professional lives and can benefit from vocational counseling and physical and occupational therapy.

Prenatal diagnosis

Prenatal testing to determine whether an unborn child is affected is possible if a specific ALD mutation has been identified in a family. This testing can be done at 10–12 weeks gestation by a procedure called chorionic villus sampling (CVS) which involves removing a tiny piece of the placenta and examining the cells. It can also be done by **amniocentesis** after 14 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it and those who are interested in learning more should check with their doctor or genetic counselor. Couples interested in these options should have **genetic counseling** to carefully explore all of the benefits and limitations of these procedures.

An experimental procedure, called preimplantation diagnosis, allows a couple to have a child that is unaffected with the genetic condition. This procedure is only possible for those families in which a mutation in the ALD gene has been identified. Those interested in learning more about this procedure should check with their doctor or genetic counselor.

Prognosis

The prognosis for people with ALD varies depending on the type of ALD. Those diagnosed with childhood ALD usually have a very rapid course. Symptoms usually progress very fast and these children typically become completely incapacitated and die within three to five years of the onset of symptoms.

The symptoms of AMN progress slowly over decades. Most affected individuals have a normal lifespan.

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Karen M. Krajewski, MS, CGC

A-gammaglobulinemia tyrosine kinase *see* **Bruton A-gammaglobulinemia tyrosine kinase (BKT)**

Aganglionic megacolon *see* **Hirschsprung disease**

Agenesis of clavicales and cervical vertebral and talipes equinovarus *see* **Crane-Heise syndrome**

Aicardi syndrome

Definition

Aicardi syndrome is a rare genetic disorder that causes defects of the eyes and brain. It is believed to be an X-linked dominant genetic trait. Aicardi syndrome is named after Dr. Jean Aicardi, who first described this syndrome in 1965.

Description

Aicardi syndrome is an X-linked dominant genetic condition primarily found in females because males with the disease do not survive to birth. It is alternately called Agenesis of Corpus Callosum (ACC) with Chorioretinal Abnormality because of the associated abnormal formation of the connection between the right and left hemispheres of the brain (the corpus callosum) and abnormal development of the choroid and retinal sections of the eye.

The eye is composed of three layers: the sclera, the choroid, and the retina. The sclera is the tough white outer coat of the eyeball; it is unaffected in individuals with Aicardi syndrome. The choroid is the middle layer of the eye. It serves to nourish the retina and absorb scattered light. The retina is the inner, light-sensitive, layer of the eye. The retina receives the image produced by the lens and contains the rods and cones that are responsible for color vision. Both the choroid and the retina are abnormally formed in individuals affected with Aicardi syndrome.

Genetic profile

The location of the **gene** mutation responsible for Aicardi syndrome has been localized to Xp22.3. At or near this same locus is the gene responsible for **micropthalmia with linear skin defects** (MLS) and the gene responsible for **Goltz syndrome**. Because only one male has ever been diagnosed with Aicardi syndrome, it is assumed that Aicardi syndrome is dominant and X-linked with near 100% fetal mortality in males. Nearly all of the cases of Aicardi syndrome are believed to result from *de novo* mutations (new mutations that occur after conception) since parents of affected individuals have normal **chromosomes**.

Demographics

Approximately 300 to 500 individuals, all female except for one, have been diagnosed with Aicardi syndrome worldwide. Aicardi syndrome is not associated with any particular sub-populations. It appears with equal frequency in all races and across all geographies. Because it is an X-linked dominant trait, it is observed almost exclusively in females.

Signs and symptoms

Aicardi syndrome is characterized by abnormalities of the connection between the left and right hemispheres of the brain (the corpus callosum), infantile spasms in affected infants and seizures in older affected individuals, developmental delays, lesions and other abnormalities of the eye, and possible other defects in the brain such as holes where healthy brain tissue should be (brain cysts) and an enlargement of the connecting cavities (ventricles) of the brain. It is these abnormalities of the brain, including the corpus callosum, that lead to the observable symptoms of seizures and developmental delays. Aicardi syndrome may also be complicated by brain tumors, benign tumors of the scalp (lipomas) and **cancer** of the blood vessels (angiosarcoma).

The onset of infantile spasms in individuals affected with Aicardi syndrome is generally observed between the third and fifth months of life. It is at this time that the final connections (neural synapses) are made in the

KEY TERMS

Absence seizure—A brief seizure with an accompanying loss of awareness or alertness.

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

***De novo* mutation**—Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

Focal seizure—A seizure that causes a brief and temporary change in movement, sensation, or nerve function.

Grand mal seizure—A seizure that causes a loss of consciousness, a loss of bladder control, generalized muscle contractions, and tongue biting.

Infantile spasms—The form of grand mal or focal seizures experienced by infants prior to the development of many voluntary muscular controls.

Post-ictal state—A period of lethargy, confusion, and deep breathing following a grand mal seizure that may last from a few minutes to several hours.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Retinal lacunae—Small abnormal cavities or holes in the retina.

developing human brain. These infantile spasms are a form of the full seizures that are experienced by older affected individuals. A seizure is the result of sudden abnormal electrical activity in the brain. This electrical activity can result in a wide variety of clinical symptoms including muscle twitches; tongue biting; fixed, staring eyes; a loss of bladder control resulting in involuntary urination; total body shaking (convulsions); and/or loss of consciousness.

There are several types of seizures. Focal, or partial, seizures are characterized by a brief and temporary change in movement, sensation, or nerve function. Examples of this type of seizure include drooling, head turning, eye movements, lip biting, or rhythmic twitching of muscles. Focal seizures usually cause no change in awareness or alertness. An absence seizure is a brief seizure with an accompanying loss of awareness or alertness such as a staring spell. Focal and absence seizures are types of petit mal seizures. A grand mal seizure is characterized by a loss of consciousness, a loss of bladder control, generalized muscle contractions, and tongue biting. Grand mal seizures are also followed by a period of lethargy, confusion, and deep breathing (post-ictal state) that may last from a few minutes to several hours.

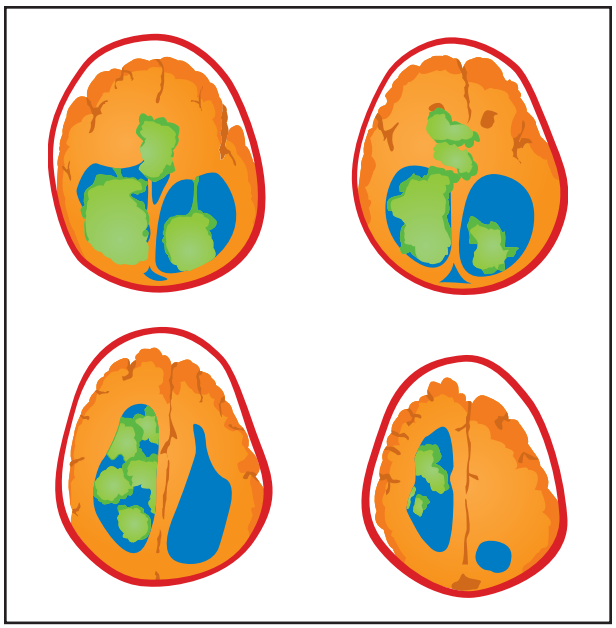
Individuals affected with Aicardi syndrome also have vision problems including blindness. These vision problems are the result of abnormal development of the two inner layers of the eye (the choroid and the retina). The most common type of malformation in the eyes of individuals with Aicardi syndrome is the appearance of small cavities or holes in the retina (retinal lacunae). Instances of small eyes (micropthalmia) and missing structures of the eye (**coloboma**) are also common.

Diagnosis

Aicardi syndrome is generally first diagnosed in affected individuals between the ages of three and five months. It is at this age that the final connections in the brain are completed. Once these connections are completed in an affected individual, this individual will begin to have infantile spasms. These spasms are akin to seizures in older children. Infantile spasms combined with defects of the retina and choroid of one eye or both eyes is sufficient evidence for the diagnosis of Aicardi syndrome. Magnetic resonance imaging (MRI) can confirm the brain malformations including the absence of the corpus callosum. Prenatal diagnosis is not yet available, but connection to the Xp22.3 locus makes **genetic testing** for this dominant trait potentially possible.

Treatment and management

Treatment of an individual with Aicardi syndrome generally consists of seizure management, vision treatment for those individuals born with sight or partial sight, and early and continuing intervention programs for developmental delays. Because of the severe neurological damage, many individuals are unable to chew and swallow and must be fed with pureed food. The most common medications for affected individuals are anticonvulsive drugs such as valproic acid (brand names: Depakene, Valproate, Valrelease); clonazepam (brand names: Klonopin and Rivotril); phenobarbitol (available as a generic drug); and phenytoin (brand name: Dilantin).



Patients diagnosed with Aicardi syndrome may develop tumors in the tiny blood vessel masses found in the third, lateral, and fourth ventricles of the brain. The tumors, refered to as choroid plexus papillomas, are green in the images above. *(Gale Group)*

Prognosis

Aicardi syndrome is lethal in males prior to birth. The prognosis in females varies on a case-by-case basis. The estimated survival rate is 76% at six years and 40% at 14 years of age. There has been a report of a surviving individual with Aicardi syndrome in her late forties. Most individuals with Aicardi syndrome are either born blind or will become blind. Developmental delays and mental retardation are seen in all individuals affected with Aicardi syndrome ranging from mild to severe.

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Paul A. Johnson

Alagille syndrome

Definition

Alagille syndrome is a genetic condition characterized by liver disease, typical facial features, heart murmurs or defects, vertebral changes, and eye changes as well as a variety of less frequently noted features. Alagille syndrome is also called arteriohepatic **dysplasia**, cholestasis with peripheral pulmonary stenosis, syndromatic hepatic ductular hypoplasia, and Alagille-Watson syndrome.

Description

Alagille syndrome is a rare condition occurring either sporadically or in an autosomal dominant pattern of **inheritance**. Approximately 70% of cases are caused by changes in the Jagged1 **gene** on chromosome 20. However, the diagnosis of Alagille syndrome is based on clinical features and family history. Obtaining medical information about family members can be difficult as some people with Alagille syndrome are so mildly affected or have variable symptoms that the condition may go unrecognized. Prognosis depends on the extent of major organ involvement, especially of the liver, heart, and kidneys. Liver transplantation is needed in some cases. Prenatal testing is available to families in which a genetic change has been identified. The interpretation of this testing is limited by the variability of clinical features, even within the same family. People with the same genetic change can have a wide range of medical problems with varying degrees of severity.

Genetic profile

Alagille syndrome occurs sporadically in 15-56% of cases, but has been noted to follow an autosomal dominant pattern of inheritance in some families. In sporadic cases, the gene change occurred for the first time in the affected individual, and neither parent has the same gene change. In autosomal dominant inheritance, multiple generations of a family are affected with the condition. In either case, people who have the genetic change have a 50% chance to pass the altered gene on to each of their children. Since the gene is dominant, passing on one

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

First-degree relative—A parent, child or sibling is a first degree relative. First-degree relatives have one half of their genes in common.

Hemivertebra—A disorder in which one side or half of a vertebra fails to form.

Proband—The person in the family who is affected by a genetic disorder and who brings the family to the attention of a health care provider.

Second-degree relative—Aunts, uncles, nieces, nephews, grandparents, grandchildren and half siblings are second-degree relatives. These individuals have one fourth of their genes in common.

Spina bifida occulta—The failure of vertebrae to close into the neural tube without nerves protruding. This is most often asymptomatic.

copy of the gene is enough to cause symptoms. However, the condition exhibits variable expressivity. This means that different people with the condition may experience different features of the disease or levels of severity. One explanation for this is that different changes in the gene may cause different features of the syndrome. However, even in families that all have the same genetic change, different features and degrees of severity can occur. In addition, the condition is not fully penetrant. Some people who have the gene change, due to an affected parent and child, do not show any features of the disease.

Changes in a gene called the Jagged1 (Jag1) gene on the short arm of chromosome 20 have been shown to be the underlying defect in many patients. The Jag1 gene encodes a cell surface protein that plays a role in the regulation of development. The protein is active in many cell types and directs cells to their proper place in the embryo. Seventy to 75% of Alagille syndrome probands have had an identifiable change within this gene. Of that 70%, 6% have been shown to have a small deletion of a piece of the short arm of chromosome 20 (20p), which includes the Jag1 gene, using a laboratory technique called fluorescent in situ hybridization. There are a variety of other molecular changes in the gene that have been detected by sequencing the gene. Thirty percent of people with the condition do not have an identifiable change in this gene. It is possible that there are other genes that cause the disease in these families.

Demographics

Alagille syndrome is rare, occurring in one in 70,000-100,000 live births. The condition affects males and females equally. Most patients with Alagille syndrome come to medical attention in the first four months of life with jaundice, an enlarged liver, severe itching of skin, or multiple raised nodular areas on the skin.

Signs and symptoms

Liver manifestations

One of the most common and most serious symptoms of Alagille syndrome is liver disease. Liver disease occurs in 90-100% of patients and often leads to growth delay or failure as a result of malnutrition. Because there is a reduction in the number of bile ducts in the liver, there are elevated bile acids in the blood and an arrest of bile excretion from the body. This results in jaundice, pruritus (severe skin itching), and xanthomas (raised nodules on the skin, especially at skin creases or areas of friction). Some patients have mild or no liver problems, while others have progressive liver failure.

Cardiac manifestations

Heart defects and murmurs have been noted in 85-95% of patients with Alagille syndrome. The most common type of defect is pulmonary artery stenosis, although other types of defects also occur. Many of these defects do not have clinical significance to the patient. However, complex and severe heart defects occur and are one of the more common causes of mortality in patients with Alagille syndrome.

Eye manifestations

An important diagnostic feature of Alagille syndrome is a particular eye finding called posterior embryotoxon. This is an anterior chamber defect of the eye caused by a prominent, centrally positioned Schwalbe

ring. This feature can be seen through a split lamp examination and does not affect vision. Since 56-90% of patients have this or other changes in the eye, including retinal pigmentary changes, an eye examination can aid in diagnosis.

Skeletal manifestations

A particular finding called a butterfly vertebra is associated with Alagille syndrome. The term butterfly vertebra refers to the appearance of the space around the vertebrae due to clefting or disruption of formation of a vertebra. There are usually no physical problems associated with this radiological finding. The frequency of butterfly vertebrae in this syndrome is uncertain, with estimates from 33-87% in different studies. Other skeletal malformations are also noted in these patients, such as **spina bifida** occulta and hemivertebrae. Therefore, radiological examination of the spine may aid in diagnosis.

Facial manifestations

The occurrence of particular facial features has been noted in 70-95% of patients with Alagille syndrome. The facial features include a prominent forehead, deep-set and widely spaced eyes, a pointed chin, and a straight nose with a bulbous tip. These features are more subjective, but one of the most consistent features of the diagnosis.

Other manifestations

Problems with the structure and function of kidneys have been noted with an occurrence of 40-70%. Most often symptoms are mild, but renal disease has caused mortality in severe cases. Mild delays in gross motor function have been noted in 16% of children. Most of these children were those with severe organ disease. Intracranial bleeding has also been noted with increased frequency and is associated with mortality in this syndrome.

Diagnosis

The diagnosis of Alagille syndrome is based on clinical features and can be made by the presence of liver disease plus two of the other major features. An ultrasound of the liver can rule out other causes of liver disease and a liver biopsy can determine if there is a reduction in the number of bile ducts. However, this finding occurs in other conditions as well as Alagille syndrome, and the timing of the biopsy is important. Older patients are more likely to have fewer bile ducts than patients under five years of age. An echocardiogram for heart defects, a radiological examination of the spine, blood tests for renal function, an ophthalmologic examination, and an examination of facial features are important diagnostic tools. A careful family history is also important in diagnosis. When a first- or second-degree relative has already been diagnosed with Alagille syndrome, the presence of even one feature of the condition may constitute a diagnosis.

Once a diagnosis has been made in an individual, the parents should undergo an evaluation for subtle features of the condition. If a parent is diagnosed, then evaluation for appropriate extended family members would be offered. A correct diagnosis is important since there are other syndromes that exhibit similar liver disease, heart defects, and eye findings. These syndromes are inherited in different ways, so the recurrence risk for offspring and other family members may be different.

Two different types of testing are used: flourescence in situ hybridization (FISH), which detects the small percentage of patients who have a deletion of the entire gene; and sequencing, which looks at changes within the gene. Sequencing is not clinically available. New technologies may make gene sequencing for mutations more readily available in the near future. If a genetic change is identified in the family, prenatal testing would be available through chorionic villus sampling or **amniocentesis**. However, the interpretation of this testing is difficult since the presence of a gene change does not allow one to predict the severity of the condition or which medical problems may occur.

Treatment and management

Liver transplantation is needed in 15-20% of patients. Other treatments depend on which of the other features of the condition are present and the degree of severity. Repair of heart defects is another surgical treatment needed in some cases.

Prognosis

Prognosis for Alagille syndrome is quite variable and depends on the degree of liver, heart, and kidney disease and the presence of intracranial bleeding. Overall, survival rates are 72-85%. The survival rate of those undergoing liver transplantation is 60-80%. There is currently no method to determine which patients will reach end-stage liver disease.

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Sonja Rene Eubanks

Albinism

Definition

Albinism is an inherited condition that causes a lack of pigment in the hair, skin, or eyes.

Description

People with albinism typically have white or pale yellow hair, pale skin, and light blue or gray eyes. Since their irises have little pigment, their eyes may appear pink or violet in different types of light. This is because light is being reflected from the reddish part of the retina in the back of the eye. Their skin usually does not tan and their eyes are often sensitive to light. Many have trouble with vision. Some children may be born with albinism, but develop some pigmentation as they grow older.

In albinism, the body does not produce enough of a pigment called melanin, which creates hair, skin, and eye color. Melanin protects the body by absorbing the sun's ultraviolet light. There are several types of albinism: some affect only the eyes, while others affect the skin and hair or other parts of the body.

KEY TERMS

Hermansky-Pudlak syndrome (HPS)—A rare form of albinism, most common in the Puerto Rican community, which can cause pigment changes, lung disease, intestinal disorders, and blood disorders.

Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Melanin—Pigments normally produced by the body that give color to the skin and hair.

Nystagmus—Involuntary, rhythmic movement of the eye.

Ocular albinism—A type of albinism that affects the vision.

Oculocutaneous albinism—Inherited loss of pigment in the skin, eyes, and hair.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

Types of albinism

Ocular: A form of albinism that mainly affects the eyes. People with ocular albinism have some pigmentation, but may have lighter skin, hair, and eye color than other family members. Scientists have identified five different types of ocular albinism.

X-linked ocular: This type of albinism occurs mostly in males, who inherit the **gene** from their mothers. It causes visual disabilities.

Oculocutaneous: A type of albinism that affects the hair, skin, and eyes. Researchers have classified 10 different types of oculocutaneous albinism.

Tyrosinase-negative oculocutaneous: Also known as Type 1A, this is the most severe form of albinism, marked by a total absence of pigment in hair, skin, and eyes. People with this type of albinism have vision problems and sensitivity to sunlight. They also are extremely susceptible to sunburn.

Tyrosinase-positive oculocutaneous: People with this type of albinism have light hair, skin, and eye coloration and fewer visual impairments.

Hermansky-Pudlak syndrome (HPS): This rare type of albinism is common in the Puerto Rican community. Approximately one person in every 1,800 people in Puerto Rico will be affected by it. The lack of pigmentation can vary widely. People with HPS may have white, pale yellow, or brown hair, but it always is lighter than the rest of the population. Their eyes range from blue to brown, and their skin can be creamy white, yellow, or brown. HPS also often causes visual changes, along with other physical symptoms.

Chediak-Higashi syndrome: A rare type of albinism that interferes with white blood cells and the body's ability to fight infection.

Black Locks Albinism Deafness syndrome (BADS): Another rare form of albinism identified by a black lock of hair on the forehead. BADS causes deafness from birth.

Piebaldism: Also known as partial albinism, this condition is marked by patches of white hair or lighter skin blotches on the body.

Genetic profile

Children inherit the genes for albinism from their parents. The parents may have normal pigmentation, but if both the mother and father carry a recessive gene, there is a one in four chance their child will have albinism.

A specific genetic abnormality causes tyrosinase-negative oculocutaneous albinism (Type 1A). In this type, also called "ty-neg albinism," the body is unable to convert the amino acid tyrosine into pigment. The genes for producing the enzymes related to ty-neg albinism are located on chromosome 11 and chromosome 9.

Similarly, scientists believe the gene that causes Hermansky-Pudlak syndrome is on chromosome 10. They are studying two other genes that appear to be involved in melanin pigment formation: the P gene on chromosome 15 and the ocular albinism gene on the X chromosome.

Women who carry the gene for X-linked ocular albinism may have normal vision, but they have a one in two chance of passing it on to their sons. This type of albinism occurs mainly in males because the gene that causes it is located on the X chromosome. Since males only have one X chromosome, genetic abnormalities on this chromosome will almost always be expressed.

Demographics

Albinism affects one in every 17,000 people. All racial groups, including African-Americans and Latinos are affected by albinism. Asians have the lowest incidence of this condition.

A man with albinism stands beside his normally pigmented father. *(Photo Researchers, Inc.)*

Signs and symptoms

Eye problems

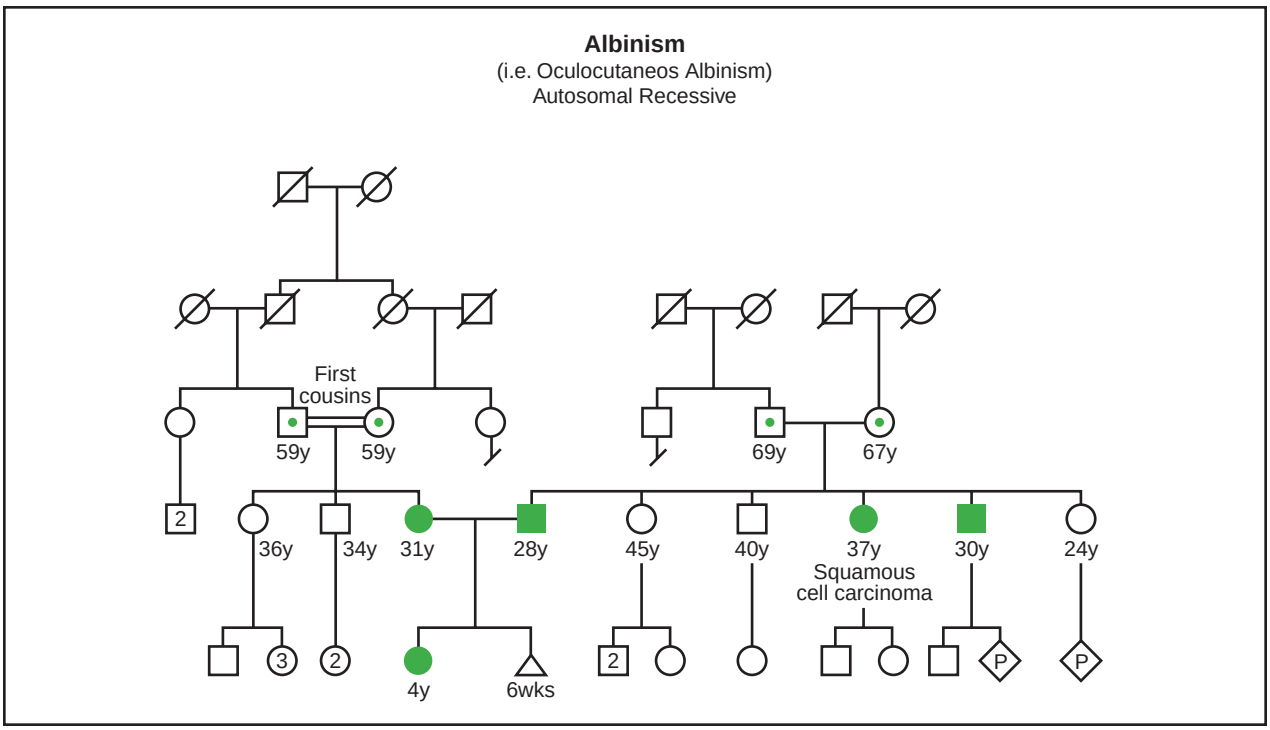
The lack of pigment in albinism causes abnormal development in the eye. For example, the iris (the colored ring around the center of the eye), which normally acts as a filter, may let too much light into the eye. Communication between the retina (the surface inside the eye that absorbs light) and the brain may also be altered in people with albinism, causing a lack of depth perception. These changes can lead to visual impairments, such as sensitivity to sunlight, near-sightedness, far-sightedness, or astigmatism (a curvature in the lens that makes it difficult to focus on objects). Other common affects of albinism on the eyes include nystagmus, a constant, involuntary shifting of the eyes from side to side; and strabismus, a disorder of the muscles in the eyes that causes a wandering eye or crossed eyes. Strabismus can interfere with depth perception.

Skin conditions

People with albinism burn easily in the sun. Since they have no pigmentation, or very little, they typically do not tan. Without adequate protection, they are more likely to develop skin cancer. Some people with albinism will have freckles, or large blotches of pigmentation, but they still will not develop a suntan.

Other rare symptoms

People with HPS may experience a variety of health problems related to their unique form of albinism. For



(Gale Group)

example, HPS can cause scarring of the lungs, or fibrosis, which leads to restrictive lung disease and causes fatigue and problems with breathing. Some people with HPS have trouble healing when they cut their skin because the disorder interferes with normal platelet function. Platelets are a component of blood needed for clotting. This complication may cause people with HPS to bruise easily, have frequent nosebleeds or trouble with bleeding gums when brushing their teeth. It also could cause heavy menstrual bleeding and excessive bleeding when a pregnant woman with HPS delivers a child. Intestinal difficulties also are associated with HPS. It can cause a condition called granulomatous colitis, which causes abdominal cramps, intestinal bleeding and diarrhea. People with HPS may also have kidney disease. Other rare forms of albinism may cause deafness or decrease the body's ability to fight infection.

Diagnosis

Physicians are able to diagnose albinism by carefully examining a person's hair, skin, eyes, and family history. Diagnostic testing usually is not necessary, but a genetic test is now available for parents who want to find out if they are carriers of ty-neg albinism. The test also can be performed on an infant by **amniocentesis** at 16 to 18 weeks gestation.

In the past, doctors used to examine a sample of the root of a person's hair, in a procedure known as a hair-bulb pigmentation test. They also tested hair for the presence of tyrosine, a substance in the body that produces melanin, to determine the type of albinism a person had. Today, however, most physicians believe these tests are not reliable and they are not often used.

To find out if a person has HPS, physicians can take a sample of their blood and examine the platelets under a microscope to look for a lack of clotting ability.

Eye doctors may be able to identify subtle eye changes in women who carry the gene for X-linked ocular albinism. While their eye color may appear normal, female carriers of this type of albinism often have a slight lack of pigment in their retinas.

Treatment and management

People with albinism must shield their sensitive eyes from the sun with UV protected sunglasses. Some find bifocals and other corrective lenses to be helpful. For those with severe forms of albinism, however, corrective lenses may not be able to overcome problems caused by developmental changes in the retina. Children with albinism may require special accommodations, such as large-print textbooks, for reading in school. If visual

impairment is severe, it may affect the individual's ability to drive.

For those with strabismus, surgery can alter their appearance, although the procedure may not significantly improve their vision. Before trying surgery, some doctors have children wear an eye patch in an attempt to strengthen the weaker eye. Eye surgery may also help reduce the involuntary eye movements associated with nystagmus, but vision will not always improve.

To prevent sun-related health problems, people with albinism must cover up with a sunscreen of SPF 20 or higher. Protective clothing, hats or visors are essential. Physicians also recommend keeping a careful watch for any changes in birth marks or moles that could become cancerous.

People with HPS should be careful to avoid aspirin, which can reduce clotting, and notify their dentist before having any dental work done. Women with HPS should alert their gynecologist or obstetrician. Some physicians recommend wearing a medical alert bracelet for the bleeding disorder. To avoid exacerbating the lung disease, people with HPS should not smoke.

Children with albinism may need extra support from family or a counselor if they are exposed to teasing or hurtful comments at school. Many families also find support groups to be helpful.

Prognosis

People with albinism can easily adapt to this condition and live healthy, productive lives. Albinism does not affect a person's lifespan, although it may lead to an increased risk of skin cancer if protective measures are not taken.

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American Council of the Blind. 1155 15th St. NW, Suite 1004, Washington, DC 20005. (202) 467-5081 or (800) 424-8666. <http://www.acb.org>.

American Nystagmus Network. PO Box 45, Jenison, MI 49429-0045. <http://www.nystagmus.org>.

Hermansky-Pudlak Syndrome Network. 39 Riveria Court, Malverne, NY 11565-1602. (800) 789-9477 or (516) 599-2077. <http://www.medhelp.org/web/hpsn.htm>.

International Albinism Center. University of Minnesota, PO Box 420, Delaware St. SE, Minneapolis, MN 55455. <http://www.cbc.umn.edu/iac>.

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Melissa Knopper

Albright syndrome *see* **McCune-Albright syndrome**

Alcoholism

Definition

Alcoholism is a chronic physical, psychological, and behavioral disorder characterized by excessive use of alcoholic beverages; emotional and physical dependence on them; increased tolerance over time of the effects of alcohol; and withdrawal symptoms if the person stops drinking.

Description

Alcoholism is a complex behavioral as well as medical disorder. It often involves the criminal justice system as well as medicine and other helping professions. Its emergence in an individual's life is affected by a number of variables ranging from age, weight, sex, and ethnic background to his or her family history, peer group, occupation, religious preference, and many other categories. Moreover, persons diagnosed with alcoholism may demonstrate considerable variety in their drinking patterns, age at onset of the disorder, and the speed of its progression.

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), distinguishes between Alcohol Dependence and Alcohol Abuse largely on the basis of a compulsive element in Alcohol Dependence that is not present in Alcohol Abuse. Some psychiatrists differentiate between so-called primary alcoholism, in which the patient has no other major psychiatric diagnosis; and secondary alcoholism, in which the problem drinking is the patient's preferred way of medicating symptoms of another psychiatric disorder, such as **depression**, **schizophrenia**, post-traumatic stress disorder, or one of the dissociative disorders. Experts in other branches of medicine tend to emphasize patterns of and attitudes toward drinking in order to distinguish between nonproblematic use of alcohol and alcohol abuse or dependence. Classification is typically based on the following five categories:

- Social drinkers. Individuals who use alcohol in minimal to moderate amounts to enhance meals or other social activities. They do not drink alone.
- Situational drinkers. These people rarely or never drink except during periods of stress. They are far more likely to drink alone than social drinkers.
- Problem drinkers. These individuals drink heavily, even when they are not under overwhelming stress. Their drinking causes some problems in their lives (e.g., DUI arrests), but they are capable of responding to warnings or advice from others.
- Binge drinkers. This type of drinker uses alcohol in an out-of-control fashion at regular intervals. The binges may be planned in advance. This pattern is a growing problem on many college campuses.
- Alcoholic drinkers. These are drinkers who have no control of any kind over their intake, and find that their lives are unmanageable.

Other factors have complicated definitions of alcoholism in the United States, including: 1) the increasing tendency to combine alcohol with other drugs of abuse, sometimes called cross-addiction; and 2) the rising rates of alcohol abuse and dependence among children under 12 years of age.

Genetic profile

Alcoholism was one of the first behavioral disorders tackled by genetic research, partly because it is a widespread problem and partly because the cost to society is so high. It has been known since the 1960s that alcoholism has a genetic component. A family history of alcoholism is presently considered the strongest risk factor for developing alcoholism. The risk increases with the number of alcoholic relatives in a person's family, the genetic closeness of the relationships, and the severity of the alcohol problems in the affected relatives. As of 2000, researchers estimate that 40%-60% of a person's vulnerability to alcoholism is genetically based. About 20% of the sons and 5% of the daughters of alcoholic parents develop the disorder, compared to 5% of men and 1% of women in the general North American population.

Alcoholism is thought to be a polygenic disorder; that is, more than one **gene** appears to be involved in its transmission. The Collaborative Study on the Genetics of Alcoholism (COGA) has pinpointed several areas in the brain that may contain genes for alcoholism. Begun in 1989, COGA has compiled a database from over 300 alcoholic families at six research sites (SUNY-Downstate, University of Connecticut, Indiana University, Washington University, University of Iowa, and University of California at San Diego). The completed mapping of the human genome is also expected to help researchers identify the specific genes that affect an individual's vulnerability to alcohol abuse.

Recent COGA findings suggest that a gene or genes on human chromosome 1 may influence vulnerability to affective disorders as well as to alcoholism. The researchers found that first-degree relatives of subjects diagnosed with depression as well as alcoholism had a higher prevalence of both disorders than relatives of subjects diagnosed with alcoholism alone.

Earlier genetic studies

MULTIGENERATIONAL STUDIES The first studies of the genetics of alcoholism were performed in the 1960s. One investigator noted that the brain wave patterns in alcoholics are lower in height (amplitude) than those of normal people and studied children of alcoholics to determine whether this brain wave pattern might be hereditary. He used two groups of boys between the ages of six and 18, one group comprised of sons of alcoholic men. More than 35% of the sons of alcoholics had the brain wave pattern characteristic of alcoholism, whereas fewer than 1% of the boys in the control group had it.

Another multigenerational brain wave study involved type 2 alcoholism, a variant of the disorder in which the alcoholic's father is always an alcoholic. This study found that 89% of the sons of type 2 alcoholics had the characteristic brain wave pattern.

Other studies of children of alcoholics have focused on the effects of alcohol on the body. A study published in 1991 reported that the sons of alcoholics perform better on tests of hand-to-eye coordination after drinking a specified amount of alcohol than the sons of nonalcoholics who had consumed the same amount. The researchers hypothesized that low sensitivity to the effects of alcohol may point to higher levels of alcohol consumption in adult life.

TWIN STUDIES Studies of twins performed in Finland and the United States indicate that people with an alcoholic monozygotic (identical) twin have a significantly higher risk of becoming alcoholics than people with alcoholic dizygotic (fraternal) twins.

STUDIES OF ADOPTED CHILDREN A longitudinal Swedish study known as the Stockholm Adoption Study was performed on children of type 2 alcoholics reared by adoptive parents. The researchers reported in the mid-1980s that 34% of these children became alcoholics in adult life, even when they had been reared by adoptive parents who abstained from alcohol.

Another longitudinal study of adopted children done at the University of Kansas Medical School found that sons of alcoholic parents were four times as likely to become alcoholics as sons of nonalcoholics, even if they had been separated from their parents shortly after birth and reared by nonrelatives with no history of problem drinking. On the other hand, the sons of nonalcoholic parents had a low rate of alcoholism in later life even if their adoptive parents were alcoholics. Studies of adopted daughters yielded less clear-cut results.

STUDIES OF GENDER AND ETHNIC VARIABLES It has been known for several decades that different nations and ethnic groups have widely varying rates of alcoholism, with Ireland, the countries of the former Soviet Union, and the Baltic countries having relatively high rates. Far Eastern and Mediterranean countries (with the exception of France) have relatively low rates. With regard to Asians, researchers have found that a large proportion of the general population—as high as 50% among the Japanese and Koreans—has an aldehyde dehydrogenase deficiency, related to a variation in a gene known as the ALDH2 gene. People with this deficiency experience a disulfiram-like reaction to small amounts of alcohol, which appears to protect them from becoming alcoholics.

KEY TERMS

Acamprosate—An anti-craving medication used in Europe to reduce the craving for alcohol. It is presently undergoing tests for approval in the United States.

Disulfiram—A medication that has been used since the late 1940s as part of a treatment plan for alcohol abuse. Disulfiram, which is sold under the trade name Antabuse, produces changes in the body's metabolism of alcohol that cause headaches, vomiting, and other unpleasant symptoms if the patient drinks even small amounts of alcohol.

Ethanol—The chemical name for beverage alcohol. It is also sometimes called ethyl alcohol or grain alcohol to distinguish it from isopropyl or rubbing alcohol.

Knockout experiment—A type of genetic experiment in which researchers are able to deactivate, or knock out, a gene that may influence a particular trait, such as vulnerability to alcohol.

Longitudinal study—A type of research project in which the same subjects are interviewed repeatedly at intervals over a period of time.

Microarray—An ordered arrangement of many different genes on a glass slide or silicon chip. Microarrays allow researchers to study large numbers of genes simultaneously in determining different levels of gene activity in such complex processes as the body's response to alcohol.

Naltrexone—A medication originally developed to treat addiction to heroin or morphine that is also used to treat alcoholism. It works by reducing the craving for alcohol rather than by producing vomiting or other unpleasant reactions.

Polygenic—A trait, characteristic, condition, etc. that depends on the activity of more than one gene for its emergence or expression.

Telescoping—A term sometimes used to describe the relatively rapid progression of alcoholism in women, even though women usually begin to drink heavily at later ages than men do.

Transgenic experiment—A genetic experiment in which a gene can be added to a laboratory animal's genetic material. The behavior of the altered animal can be compared with the behavior of an unaltered animal to help pinpoint the role of the gene in affecting it.

Studies of women indicate that Caucasian women in the United States have a higher rate of aldehyde dehydrogenase deficiency than men. It is not known, however, how important this factor is in explaining the overall lower rate of alcoholism among women. One study of Australian twins found that the variation in the ALDH2 gene that decreases the risk of alcoholism in men does not have this protective effect in women. Race and ethnicity affect both patterns of alcohol consumption in women and physical vulnerability to the effects of alcohol. Although African American women and Caucasian women are equally likely to be heavy drinkers, African American women are more likely than Caucasians to abstain from alcohol (46% versus 34%). Among Hispanic women, American-born Hispanics are more likely to be moderate or heavy drinkers than Hispanic immigrants.

Another important variable in assessing the role of ethnicity in alcohol dependence is educational attainment. According to one 2000 study, low levels of educational attainment are correlated with alcohol dependence among African Americans, while high levels of education are associated with alcohol dependence among Caucasians. Another 2000 study found that dropping out of high school was associated with an increased risk of alcohol abuse among both groups, while entering college without completing the course of studies was associated with a higher rate of alcohol abuse only in Caucasians. The long-term effects of educational level on alcohol dependence in different subcultures, however, require further study.

STUDIES OF BRAIN TISSUE In 1990, researchers at UCLA and the University of Texas studied tissue samples from the brains of 70 deceased persons (men and women from a variety of ethnic groups); half the samples were from known alcoholics. Of the tissue samples from alcoholics, 69% had an abnormal gene for dopamine reception whereas 80% of the nonalcoholics' samples had a normal gene. Dopamine is a neurotransmitter associated with a sense of pleasure; its receptor gene is located on human chromosome 11. The researchers speculated that the atypical form of the gene may direct the formation of defective dopamine receptors in the brain, which in turn may cause the person to crave alcohol and other substances that increase the body's dopamine production.

Newer genetic engineering techniques

The introduction of newer techniques developed in the 1990s has contributed to a greater understanding of the complexity of the genetic transmission of alcoholism in humans.

KNOCKOUT AND TRANSGENIC EXPERIMENTS Newer genetic engineering techniques that were developed in the 1990s allow researchers to deactivate, or knock out, a gene that is thought to be involved in sensitivity to or desire for alcohol. Alternately, researchers can insert a gene into an animal's genetic material, thus producing transgenic offspring. Several knockout experiments have produced strains of mice with a craving for alcohol that can be traced to specific proteins in the brain. Both knockout and transgenic experiments on mice have confirmed the hypothesis that low sensitivity to the effects of alcohol appears to be related to a high preference for consuming alcohol.

MICROARRAYS Microarrays are glass slides or silicon chips with selected genes—as many as 10,000—arranged on them for scanning by an automated system. Because alcoholism is a polygenic disorder, and because genes often change their levels of activity in response to the effects of alcohol, microarrays allow researchers to track the activity levels of a large number of genes simultaneously. As of 2001, it is thought that changes in gene function may be a factor in the human brain's long-term adaptations to heavy drinking.

Demographics

Health professionals estimate that 70% of the adult population of the world's developed countries drink alcohol, with a slightly higher rate (75%) in the United States. Of those who drink, about 10% will become alcoholics. This group of heavy drinkers spends more time in the doctor's office or the ER than most other adults; it is estimated that 20% of hospital inpatients and 15% of outpatients have alcohol problems. There is a definite gender imbalance in alcoholism, with males predominating by a ratio of 4:1 or 3:1. According to a 2000 report from the Centers for Disease Control, 22.3% of men are binge drinkers, compared to 6.7% of women. On the other hand, evidence accumulating in the 1990s suggests that the gender ratio is dropping among younger drinkers. A 1997 U.S. Department of Health and Human Services (DHHS) survey found that the current use of alcohol among women is highest in the 26 to 34 age group, and that binge and heavy drinking are highest among 18- to 25-year-olds. The smallest sex differences in heavy drinking are for youths aged 12 to 17 (2% of boys and 1% of girls in 1993; 2% of boys and 1.5% of girls younger than 12 in 1999).

Studies of women alcoholics indicate that women are at higher risk than men for serious health problems related to alcoholism. Because women tend to metabolize alcohol more slowly, have a lower percentage of body water and a higher percentage of body fat than men, they

develop higher blood alcohol levels than men at a given amount of alcohol per pound of body weight. Thus, even though women typically begin to drink heavily at a later age than men, they often become dependent on alcohol much more rapidly. This relatively speedy progression of alcoholism in women is called telescoping.

At the other end of the age distribution, alcoholism among the elderly appears to be on the increase as well as underdiagnosed. Confusion and other signs of intoxication in an elderly person are often misinterpreted as side effects of the patient's other medications. In addition, many older people turn to alcohol to medicate feelings of depression. It is estimated, as of 1999, that 15% of older women in treatment for depression are alcoholics. The elderly are at higher risk for becoming dependent on alcohol than younger people because their bodies do not absorb alcohol as efficiently; a 90-year-old who drinks the same amount of alcohol as a 20-year-old (of the same sex) will have a blood alcohol level 50% higher.

Signs and symptoms

The symptoms of alcohol intoxication often include talkativeness and a positive mood while the drinker's blood alcohol level is rising, with depression and mental impairment when it is falling. Blood alcohol concentration (BAC) produces the following symptoms of central nervous system (CNS) depression at specific levels:

- 50 mg/dL: feelings of calm or mild drowsiness
- 50-150 mg/dL: loss of physical coordination. The legal BAC for drivers in most states is 100 mg/dL or lower.
- 150-200 mg/dL: loss of mental faculties
- 300-400 mg/dL: unconsciousness
- Over 400 mg/dL: may be fatal.

The symptoms of long-term heavy consumption of alcohol may take a variety of different forms. In spite of a long history of use for "medicinal" purposes, alcohol is increasingly recognized to be toxic to the human body. It is basically a CNS depressant that is absorbed into the bloodstream, primarily from the small intestine. Regular consumption of large amounts of alcohol can cause irreversible damage to a number of the body's organ systems, including the cardiovascular system, the digestive tract, the central nervous system, and the peripheral nervous system. Heavy drinkers are at high risk of developing stomach or duodenal ulcers, cirrhosis of the liver, and cancers of the digestive tract. Many alcoholics do not eat properly, and often develop nutritional deficiency diseases as well as organ damage.

Women are at higher risk for serious alcohol related health problems then men. Because women tend to metabolize alcohol more slowly, have a lower percentage of body water and a higher percentage of body fat than men, they develop higher blood alcohol levels than men at a given amount of alcohol per pound of body weight. *(Custom Medical Stock Photo, Inc.)*

In addition to physical symptoms, most alcoholics have a history of psychiatric, occupational, financial, legal, or interpersonal problems as well. Alcohol misuse is the single most important predictor of violence between domestic partners as well as intergenerational violence within families. In 1994 (the latest year for which statistics are available), 79% of drivers over age 25 involved in fatal automobile accidents were intoxicated. In the states that provided data in 1994 for arrests for driving while impaired (DWI) by alcohol, about one-third of the arrested drivers had previous DWI citations. Since the early 1990s, most states have passed stricter laws against alcohol-impaired driving. These laws include such provisions as immediate license suspension for the first DWI arrest and lowering the legal blood alcohol limit to 0.08 g/dL for adults and 0.02 g/dL for drivers under 21. Penalties for repeated DWI citations include prison sentences; house arrest with electronic monitoring; license plates that identify offending drivers; automobile confiscation; and putting a special ignition interlock on the offender's car.

Diagnosis

The diagnosis of alcoholism is usually based on the patient's drinking history, a thorough physical examination, laboratory findings, and the results of psychodiagnostic assessment.

Patient history and physical examination

A physician who suspects that a patient is abusing or is dependent on alcohol should give him or her a complete physical examination with appropriate laboratory tests, paying particular attention to liver function and the nervous system. Physical findings that suggest alcoholism include head injuries after age 18; broken bones after age 18; other evidence of blackouts, frequent accidents, or falls; puffy eyelids; flushed face; alcohol odor on the breath; shaky hands; slurred speech or tongue tremor; rapid involuntary eye movements (nystagmus); enlargement of the liver (hepatomegaly); hypertension; insomnia; and problems with impotence (in males). Severe memory loss may point to advanced alcoholic damage to the CNS.

Diagnostic questionnaires and checklists

Since some of the physical signs and symptoms of alcoholism can be produced by other drugs or disorders, screening tests can also help to determine the existence of a drinking problem. There are several assessment instruments for alcoholism that can be either self-administered or administered by a clinician. The so-called CAGE test is a brief screener consisting of four questions:

- Have you ever felt the need to *cut down* on drinking?
- Have you ever felt *annoyed* by criticism of your drinking?
- Have you ever felt *guilty* about your drinking?
- Have you ever taken a morning *eye opener*? One "yes" answer should raise a suspicion of alcohol abuse; two "yes" answers are considered a positive screen.

Other brief screeners include the Alcohol Use Disorder Identification Test, or AUDIT, which also highlights some of the physical symptoms of alcohol abuse that doctors look for during a physical examination of the patient. The Michigan Alcoholism Screening Test, or MAST, is considered the diagnostic standard. It consists of 25 questions; a score of five or higher is considered to idicate alcohol dependency. A newer screener, the Substance Abuse Subtle Screening Inventory, or SASSI, was introduced in 1988. It can be given in either group or individual settings in a paper-and-pencil or computerized format. The SASSI is available in an adolescent as well as an adult version from the SASSI Institute.

According to one 1998 study, some brief screeners may be inappropriate for widespread use in some subpopulations because of ethnic and sex bias. The CAGE questionnaire often yielded inaccurate results when administered to African American men and Mexican American women. The AUDIT does not appear to be affected by ethnic or gender biases. Another study of the use of alcohol screening questionnaires in women found that the AUDIT was preferable to the CAGE questionnaire for both African American and Caucasian women.

Laboratory tests

Several laboratory tests can be used to diagnose alcohol abuse and evaluate the presence of medical problems related to drinking. These tests include:

- Full blood cell count. This test indicates the presence of anemia, which is common in alcoholics. In addition, the mean corpuscular volume (MCV) is usually high in heavy drinkers. An MCV higher than 100 fL suggests alcohol abuse.
- Liver function tests. Tests for serum glutamine oxaloacetic transaminase (SGOT) and alkaline phosphatase can indicate alcohol-related injury to the liver. A high level (>30 units) of gamma-glutamyltransferase (GGT) is a useful marker because it is found in 70% of heavy drinkers.
- Blood alcohol levels.
- Carbohydrate deficient transferrin (CDT) tests. This test should not be used as a screener, but is useful in monitoring alcohol consumption in heavy drinkers (those who consume >60 grams of alcohol per day). When CDT is present, it indicates regular daily consumption of alcohol.

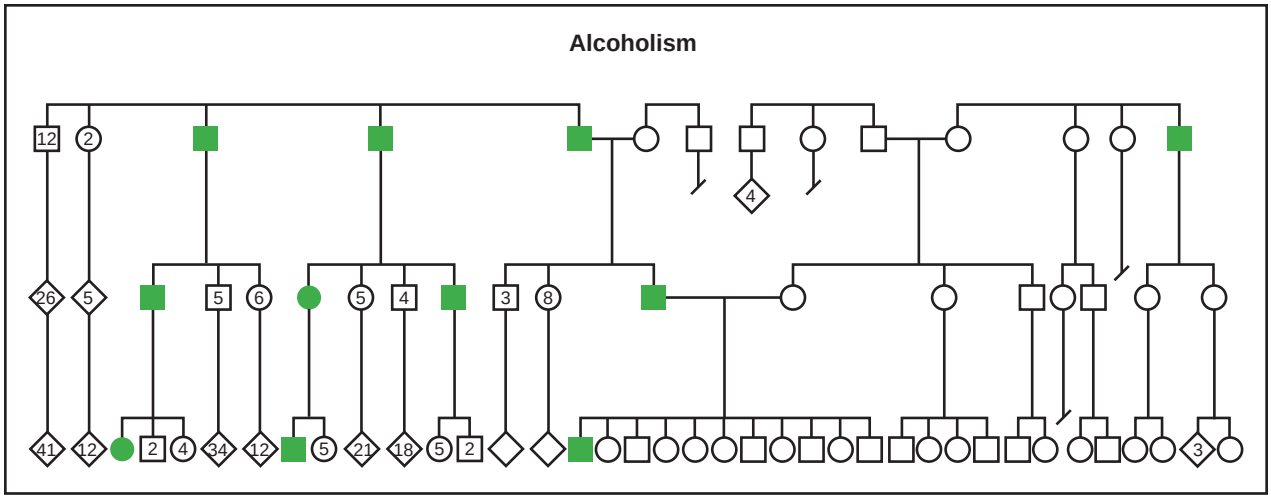
The results of these tests may not be accurate if the patient is abusing or dependent on other substances.

Treatment and management

Because alcoholism is a complex disorder with social and occupational as well as medical implications, treatment plans usually include a mix of several different approaches.

Medications

Most drugs that are now being used to treat alcoholism fall into one of two groups: those that restrain the desire to drink by producing painful physical symptoms if the patient does drink; and those that appear to reduce the craving for alcohol directly. Several medications in the second category were originally developed to treat



(Gale Group)

addiction to opioid substances (e.g., heroin and morphine).

ALCOHOL-SENSITIZING MEDICATIONS The most commonly used alcohol-sensitizing agent is disulfiram (Antabuse), which has been used since the 1950s to deter alcoholics from drinking by the threat of a very unpleasant physical reaction if they do consume alcohol. The severity of the disulfiram/ethanol reaction, or DER, depends on the amount of alcohol and disulfiram in the blood. The symptoms of the reaction include facial flushing, rapid heart beat, palpitations, difficult breathing, lowered blood pressure, headaches, nausea, and vomiting.

A DER results when the drinker consumes alcohol because disulfiram inhibits the functioning of an enzyme called aldehyde dehydrogenase. This enzyme is needed to convert acetaldehyde, which is produced when the body begins to oxidize the alcohol. Without the aldehyde dehydrogenase, the patient's blood level of acetaldehyde rises, causing the symptoms associated with DER.

Another alcohol-sensitizing agent is calcium carbimide, which is marketed in Canada under the brand name Temposil. Temposil has been used clinically although it has not been approved by the FDA for use in the United States as of 2001. Calcium carbimide produces physiological reactions with alcohol similar to those produced by disulfiram, but the onset of action is far more rapid and the duration of action is much shorter.

ANTI-CRAVING MEDICATIONS One medication that has been studied in recent years for the treatment of alcoholism is naltrexone, which appears to reduce the craving for alcohol. In addition, naltrexone, which is sold under the brand names Trexan and ReVia, appears to cause few side effects. One 1992 study suggested that naltrexone-treated alcoholics who did have one or two drinks were less likely to continue drinking. Naltrexone has been the subject of a number of clinical trials in the United States; as of August 2000, 10 out of 30 NIH-sponsored clinical trials were studies of naltrexone. On the other hand, a review of medications presented to the National Institute on Alcohol and Alcohol Abuse (NIAAA) in November 1999 concluded that the effectiveness of naltrexone in the treatment of alcoholism appears to be limited.

An anti-craving drug that is presently approved for use in the European Community, acamprosate (calcium acetyl-homotaurinate), has no psychotropic side effects nor any potential for abuse or dependence. Although acamprosate is being used in clinical trials in the United States as of 2000, its effects are unclear. It appears to reduce the frequency of drinking, but its effects on enhancing abstinence from alcohol are no greater than those of naltrexone. In addition, acamprosate does not appear to enhance the effectiveness of naltrexone if the drugs are given in combination.

Psychosocial treatment options

Most alcoholics are treated with a variety of psychosocial approaches, including regular attendance at Alcoholics Anonymous (AA) meetings, group therapy, marital or family therapy, so-called community-based approaches, social skills training, relapse prevention, and stress management techniques. Insight-oriented individual psychotherapy by itself is ineffective with the majority of alcoholics.

The most effective psychosocial treatments of alcohol dependence incorporate a cognitive-behavioral approach. Relapse prevention utilizes cognitive-behav-

ioral approaches to identifying high-risk situations for each patient and restructuring his or her perceptions of the effects of alcohol as well as of the relapse process. Network therapy, which combines individual cognitive-behavioral psychotherapy with the involvement of the patient's family and peers as a group support network, is a newer approach to alcohol dependence. One recent study found that while cognitive-behavioral therapy is effective in treating alcohol dependence, the reasons that are usually offered to explain its effectiveness should be reexamined.

Prognosis

The prognosis for recovery from alcoholism varies widely. The usual course of the disorder is one of episodes of intoxication beginning in adolescence, with full-blown dependence by the mid-20s to mid-30s. The most common pattern is one of periodic attempts at abstinence alternating with relapses into uncontrolled drinking. On the other hand, it is thought that as many as 20% of persons diagnosed as alcohol-dependent achieve long-term sobriety even without medical treatment. As of 2001, it is difficult to compare the outcomes of the various treatment approaches to alcoholism, in part because their definitions of "success" vary. Some researchers count only total abstinence from alcohol as a successful outcome, while others regard curtailed drinking and better social adjustment as indicators of success. The role of genetic factors in the prognosis is still disputed. Available evidence suggests that such factors as the presence of a spouse, partner, or close friend in the alcoholic's life, or religious commitment, can outweigh genetic vulnerability to the disorder.

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ORGANIZATIONS

Alcoholics Anonymous World Services. PO Box 459, Grand Central Station, New York, NY 10163. (212) 870-3400.

American Psychiatric Association. 1400 K St. NW, Washington, DC 20005. (202) 682-6220.

National Clearinghouse for Alcohol and Drug Information. PO Box 2345, Rockville, MD 20847. (800) 729-6686.

National Council on Alcoholism and Drug Dependence Hopeline. 12 West 21st St., New York, NY 10010. (800) 622-2255.

National Institute on Alcohol Abuse and Alcoholism. 5600 Fishers Lane, Rockville, MD 20852.

WEBSITES

American Psychiatric Association. <http://www.psych.org>.

National Institute of Mental Health. <http://www.nimh.nih.gov>.

National Institute on Alcohol and Alcohol Abuse (NIAAA). <http://www.niaaa.org>.

Rebecca J. Frey, PhD

Aldrich syndrome *see* **Wiskott-Aldrich syndrome**

Alkaptonuria

Definition

Alkaptonuria is a rare, inherited disorder characterized by urine that turns dark when exposed to air, dark pigmentation of the cartilage and other tissues, and arthritis.

Description

Alkaptonuria (AKU) (sometimes spelled alcaptonuria) is a disorder in which a substance called homogentisic acid (HGA) accumulates in cells and connective tissues throughout the body. Large amounts of HGA also are excreted in the urine. In a process known as ochronosis, deposits of HGA form dark pigments in the skin, joints, and other tissues of the body. Over the long term, ochronosis leads to ochronotic arthritis, which is a painful inflammation and stiffening of the joints. AKU is also known as homogentisic acid oxidase deficiency, ochronosis, alkaptonuria ochronosis, or ochronotic arthritis.

History

The black urine that characterizes AKU has been recognized throughout history. It sometimes was considered to be a bad omen. The dark pigmentation of ochronosis has been identified in an Egyptian mummy from 1500 B.C.

AKU was one of the first inherited disorders to be identified as a deficiency in a single enzyme in one pathway of the body's metabolism. In 1902, Sir Archibald Garrod, after consultation with the famous geneticist William Bateson, proposed that the **inheritance** of AKU could best be described by Gregor Mendel's theory of the inheritance of recessive characteristics. These are inherited traits expressed in some of the offspring of parents who both carry the trait. The parents may or may not express the trait. In 1908, Garrod coined the term "inborn error of metabolism" to describe AKU and three other metabolic disorders. Furthermore, he suggested that AKU was due to a deficiency in a specific enzyme, a protein that catalyzes one step of a metabolic pathway.

Homogentisic acid

During normal metabolism, the 20 common amino acids, that are the building blocks of enzymes and other proteins, are broken down into simpler substances. This process provides energy for the body. The amino acids phenylalanine and tyrosine are converted to simpler substances in a series of eight steps. Each step in this path-

way occurs through the action of a different enzyme. The first step in the pathway converts phenylalanine to tyrosine. The inherited disorder known as phenylketonuria results from a deficiency in the enzyme that carries out this first step.

AKU results from a deficiency in an enzyme called homogentisate 1,2-dioxygenase (HGD). This enzyme also is called homogentisic acid oxidase. It is responsible for the fourth step in the breakdown of phenylalanine and tyrosine, the conversion of HGA to 4-maleylacetoacetic acid. When there is a deficiency in active HGD, as in AKU, HGA cannot be broken down further. It accumulates in cells and tissues throughout the body, and large amounts of HGA are excreted in the urine.

Oxygen causes HGA molecules to combine with each other to form a very large molecule called a polymer. This polymer is a dark pigment similar to melanin, the pigment responsible for skin color. This pigment is formed in the tissues of the body, as well as in urine exposed to the oxygen in air. Oxygen can also convert HGA into a toxic substance called benzoquinone acetic acid.

HGA is excreted very quickly. In general, levels of HGA are kept quite low in individuals with AKU. Nevertheless, over time, large quantities of HGA, either as individual molecules or as a polymer, are deposited in the cartilage (the flexible tissue of the joints and other bony structures) and in other connective tissues of the body.

Granules of HGA pigment collect around collagen. This is the protein that makes up the fibers of connective tissues. Collagen is the most abundant protein in the body. It is a major structural component of cartilage, bone, tendons, ligaments, and blood vessels. Collagen also forms an important structural layer beneath the skin, and it holds together the cells of various tissues. The accumulation of HGA in connective tissues interferes with the body's ability to make new collagen. As a result, collagen fibers throughout the body are weakened. In particular, HGA weakens the collagen fibers in the cartilage of the joints.

Ochronosis

Initially, an ochre or yellowish-colored HGA pigment is deposited in the tissues of individuals with AKU. Over a period of years, the cartilage, bones, and skin begin to turn a slate-blue or blue-black color. This pigmentation, or ochronosis, of the tissues eventually leads to a serious form of arthritis. Furthermore, as the HGA polymer accumulates, inflammation occurs. This causes calcium to be deposited in the joints in a process called calcification.

Genetic profile

AKU is an autosomal recessive disorder. It is autosomal because the **gene** encoding the HGD enzyme is located on chromosome 3, rather than on either of the X or Y sex **chromosomes**. AKU is a recessive trait because it only occurs when an individual has two copies of the defective gene, one inherited from each parent. The two defective HGD genes do not need to carry the same mutations. If the two mutations are identical, the individual is a homozygote. If the two mutations are different, the affected individual is called a compound heterozygote.

In individuals with a single defective HGD gene, at least 50% of the HGD enzyme has normal activity. These individuals have no symptoms of AKU. However, they are carriers of AKU and can pass the gene on to their offspring.

All of the offspring of two parents with AKU will inherit the disorder. All of the offspring of one parent with AKU and one parent with a single defective HGD gene will inherit at least one defective HGD gene. These offspring have a 50% chance of inheriting two defective genes and developing AKU. The offspring of one parent with AKU and one parent with normal HGD genes will inherit a defective gene from the affected parent, but will not develop AKU. The offspring of parents who both carry one defective HGD gene have a 50% chance of inheriting one defective HGD gene. They have an additional 25% chance of inheriting two such genes and developing AKU. Finally, the children of one parent with a single defective HGD gene and one parent with normal HGD genes have a 50% chance of inheriting the defective gene, but will not develop AKU.

A large number of different mutations have been identified in the HGD gene. These changes reduce or destroy the activity of the HGD enzyme. Mutational hot spots have also been identified in the gene. These are regions of the gene in which mutations are particularly likely to occur.

Demographics

As a recessive disorder, AKU requires two copies of the defective gene, one inherited from each parent. Thus, AKU is much more common in the offspring of couples who are related to each other, such as first or second cousins. As an autosomal disorder, AKU occurs equally among males and females. However, in general, the symptoms of arthritis appear at an earlier age in males and tend to be more severe than in females. The reason for this difference is not known.

AKU occurs with equal frequency among various races; however, the frequency varies substantially among different populations. It is most common in geographically isolated populations. The worldwide prevalence of AKU is estimated at between one in 100,000 and one in 250,000 individuals. However, some estimates are as low as one in a million individuals and, in the United States, AKU frequency is estimated to be only one in four million.

AKU occurs with particularly high frequency in the Dominican Republic, Slovakia, and the Czech Republic. The frequency has been reported to be as high as one in 19,000 live births in Slovakia. The frequency of AKU is particularly low in Finland. Certain mutations occur only in HGD genes from Slovakia. Two specific mutations occur in 50% of all Slovakians with AKU. Other mutations in HGD appear to be unique to the Finnish population.

Signs and symptoms

Early symptoms

Often, the first sign of AKU is the dark staining of an infant's diapers from the HGA in the urine. However, a significant number of AKU-affected individuals do not have blackened urine, particularly if their urine is acidic. Other than darkened urine, AKU generally has no symptoms throughout childhood and early adulthood. Nevertheless, pigment is being deposited in the tissues throughout the early years. Occasionally, black ear wax and pigmentation under the arms may develop before the age of 10.

Ochronosis

Ochronosis, the pigmentation of the cartilage, usually does not become apparent until the fourth decade of life. Small rings or patches of slate-blue, gray, or black discoloration of the white, outer membranes of the eyeballs are one of the first visible symptoms. This usually begins when affected individuals are in their 30s. Thickening and discoloration of the cartilage of the ear usually begins in the following decade. This is indicative of the widespread staining of cartilage and other tissues. The ear cartilage may become stiff, irregularly shaped, and calcified (hardened with deposits of calcium).

Discoloration of the skin is due to the depositing of ochronotic pigment granules in the inner layer of the skin and around the sweat glands. The outer ear and nose may darken with a bluish tint. Pigmentation also may be visible on the eyelids, forehead, and armpits. Where the skin is exposed to the sun, and in the regions of the sweat glands, the skin may become speckled with blue-black discoloration. Sweat may stain clothes brown. Fingernails may become bluish.

The ochronotic effects of AKU on the cartilage and tendons are most visible on parts of the body where the connective tissues are closest to the skin. Pigmentation

KEY TERMS

Alkaline—Having a basic pH; not acidic.

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are "essential amino acids" which the body cannot make and must therefore be obtained from food).

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Benzoquinone acetic acid—Toxic compound that is formed when oxygen reacts with homogentisic acid.

Calcification—A process in which tissue becomes hardened due to calcium deposits.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Compound heterozygote—Having two different mutated versions of a gene.

Homogentisate 1,2-dioxygenase (HGD)—Homogentisic acid oxidase, the fourth enzyme in the metabolic pathway for the breakdown of phenylalanine.

Homogentisic acid (HGA)—2,5-Dihydroxyphenylacetic acid, the third intermediate in the metabolic pathway for the breakdown of phenylalanine.

Homozygote—Having two identical copies of a gene or chromosome.

Melanin—Pigments normally produced by the body that give color to the skin and hair.

Mendel, Gregor—Austrian monk who discovered the basic principals of hereditary.

Ochronosis—A condition marked by pigment deposits in cartilage, ligaments, and tendons.

Phenylalanine—An essential amino acid that must be obtained from food since the human body cannot manufacture it.

Polymer—A very large molecule, formed from many smaller, identical molecules.

Tyrosine—An aromatic amino acid that is made from phenylalanine.

may be visible in the genital regions, the larynx (voice box), and the middle ear. Dark-stained tendons can be seen when the hand is made into a fist.

Arthritis

The symptoms of ochronotic arthritis are similar to those of other types of arthritis. However, the large, weight-bearing joints usually are the most affected in ochronotic arthritis. These include the joints of the hips, knees, and shoulders, and between the vertebrae of the spine. The joints become stiff and difficult to move. This arthritis develops at an unusually early age. In unaffected individuals, similar arthritis usually does not develop before age 55. Men with AKU develop arthritis in their 30s and 40s. Women with AKU usually develop arthritis in their 50s.

AKU can lead to osteoarthrosis, a degenerative joint disease, and ochronotic arthropathy, which is characterized by the swelling and enlargement of the bones. Ankylosis, the adhesion of bones in the joints, also may occur. The pigment deposits may cause the cartilage to become brittle and susceptible to fragmenting. Individuals with AKU may be at risk for bone fractures.

Calcium deposits can lead to painful attacks similar to those of gout. This calcification may occur in the ear cartilage and in the lumbar disks of the lower back. The disks between vertebrae may become narrowed and eventually may collapse.

Organ damage

The coronary artery of the heart can become diseased as a result of AKU. The aortic valve of the heart may harden and narrow from calcification. Similar problems may develop with the mitral or left atrioventricular valve of the heart (mitral valvulitis). Deposits of pigment can lead to the formation of hard spots of cholesterol and fat (atherosclerotic plaques) in the arteries. This can put a person at risk for a heart attack.

Complications from the deficiency of the HGD enzyme arise primarily in the kidneys and the liver. HGD normally is most active in the kidneys, liver, small intestine, colon, and prostate. The calcification of the genital and urinary tract may lead to blockages in as many as 60% of individuals with ochronosis. Kidney stones and other kidney diseases may develop. Stones in the urine may occur in middle to late adulthood. Increasingly though, this condition is seen in children with AKU under the age of 15 and even as young as two. In men, pigment deposits may lead to stones in the prostate.

The teeth, the brain and spinal cord, and the endocrine system that produces hormones also may be affected by ochronosis. Breathing may become restricted due to the effects of ochronosis on the joints where the ribs attach to the spine. Deposits of pigment on the ear bones and on the membrane of the inner ear may lead to tinnitus, or ringing of the ears, and hearing problems.

Diagnosis

Visual diagnosis

AKU is often detected in early childhood because of the characteristic dark-staining of the urine. In adults, diagnosis usually is made on the basis of joint pain and skin discoloration. Most individuals with AKU have pigment visible in the whites of their eyes by their early 40s.

A family history of AKU helps with the diagnosis. Since many individuals with AKU have no symptoms, siblings of affected individuals should be tested for the disorder.

Identification of HGA

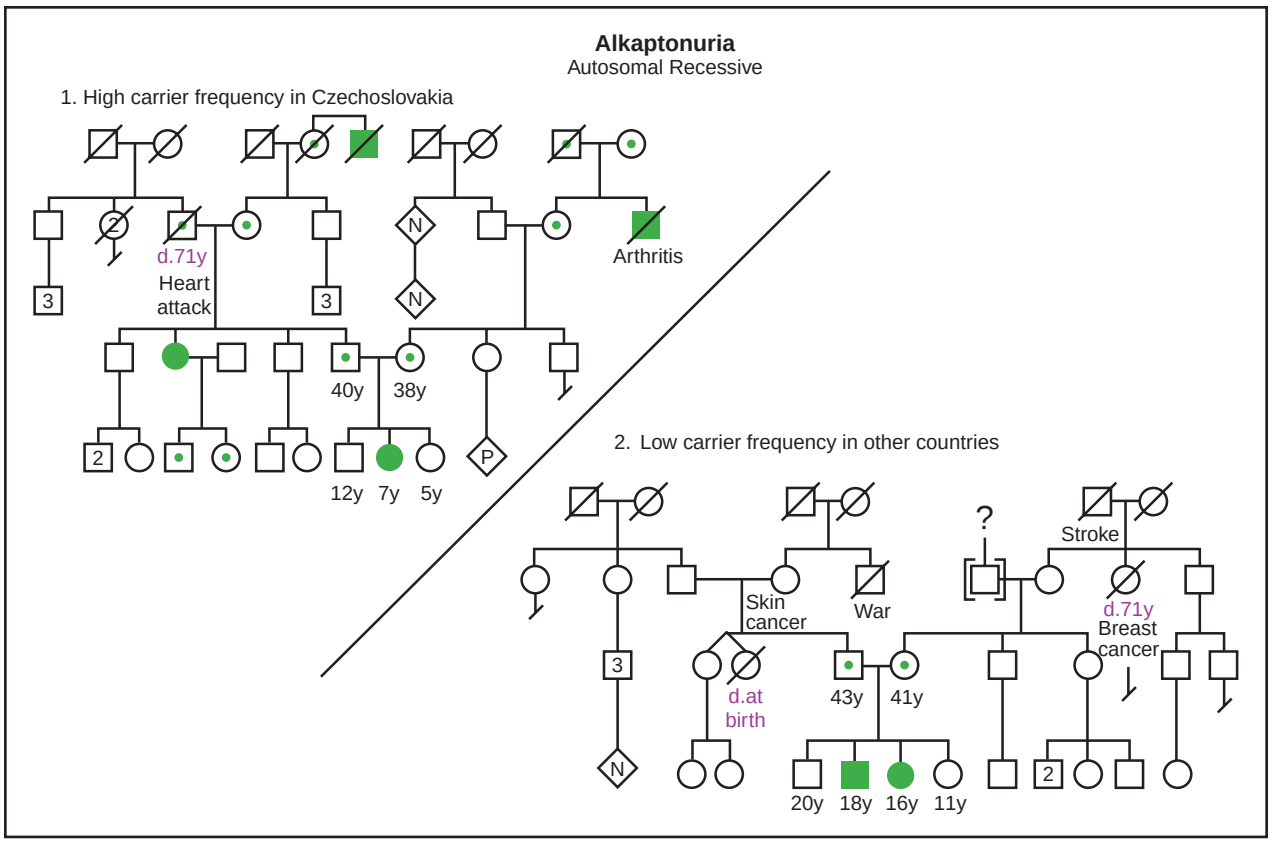
An individual with AKU may excrete as much as 4-8 g of HGA per day in the urine. There are several simple methods to test for HGA in the urine: the addition of sodium hydroxide (an alkali) to the urine will turn it dark; urine with HGA turns black when reacted with iron chloride; and alkaline urine containing HGA blackens photographic paper. In the laboratory, HGA can be identified in the urine using a technique called gas chromatography-mass spectroscopy. This technique separates and identifies the components of a mixture.

There are a number of methods for identifying HGA in the blood and tissues. These include procedures for separating HGA from other components of the blood and instruments that can detect the characteristic color of HGA. With AKU, the concentration of HGA in the blood is approximately 40 micromolar, or 40 micromoles of per liter.

Microscopic examination

With AKU, there usually is visible black staining of cartilage in various body regions, particularly the larynx, trachea (windpipe), and cartilage junctions. Heavy deposits of pigment also occur in the bronchi (the air passages to the lungs). Pigment on the inside and outside of the cells of these tissues can be seen with a microscope.

A skin biopsy, the removal of a small piece of skin, may be used to obtain tissue for examination. The tissue is stained with dyes to reveal the yellowish-brown pigment deposits on the outside of skin cells. Pigment deposits also occur in cells of the endothelium (the thin layer of cells that line blood vessels and other tissues), in the sweat glands, and in the membranes below the skin.



(Gale Group)

These pigments will not fade, even after three days in a solution of bleach.

Skeletal x rays

X-ray examination is used to detect calcification of the joints. Since many individuals with AKU do not have dark-staining urine, x-ray evidence of **osteoarthritis** may indicate a need to test for the presence of HGA in the urine. However, osteoarthritis usually affects the smaller joints; whereas ochronosis most often affects the large joints of the hips and shoulders. Spinal x rays may show dense calcification, degeneration, and fusion of the disks of the vertebrae, particularly in the lumbar region of the lower back. Chest x rays are used to assess damage to the valves of the heart.

Other procedures

Physicians may order computerized tomography (CT) scans of the brain and chest or magnetic resonance imaging (MRI) of affected joints. An electrocardiogram (ECG or EKG) may reveal signs of heart complications resulting from AKU. Kidney problems may be diagnosed by ultrasound, the use of sound waves to obtain images of an organ. Lung function tests and hearing tests may be performed to assess additional complications.

Acquired ochronosis

In addition to being a complication of AKU, ochronosis can be acquired. In the past, ochronosis developed from the repeated use of carbolic acid dressings for treating chronic skin ulcers. The prolonged use of the drug quinacrine (atabrine) can cause ochronosis, with pigmentation occurring in many of the same sites as with AKU. Ochronosis can also result from the use of bleaching creams containing hydroquinone. Certain other substances, including phenol, trinitrophenol, quinines, and benzene, can cause ochronosis. However, these forms of ochronosis do not lead to joint disease and, unlike ochronosis from AKU, are reversible.

Treatment and management

The binding of HGA to collagen fibers is irreversible. Treatment of AKU is directed at reducing the deposition of pigment and thereby minimizing arthritis and heart problems in later life.

Vitamin C

Often, high doses (about 1 gm per day) of ascorbic acid (vitamin C) are administered to older children and adults with AKU. Ascorbic acid appears to slow the formation of the HGA polymer and decrease the binding of the polymer to connective tissues. Vitamin C reduces the amount of toxic benzoquinone acetic acid in the urine. However, the amount of HGA in the urine does not decrease. Furthermore, vitamin C does not appear to interrupt the progress of the disease.

Dietary restrictions

Sometimes individuals with AKU are placed on low-protein diets. This limits the intake of phenylalanine and tyrosine from proteins. If the body has lower amounts of phenylalanine and tyrosine to break down, less HGA will be formed. However, both of these amino acids are necessary for making proteins in the body. Furthermore, phenylalanine is an essential amino acid that must be obtained from food, since the human body cannot produce it. Adult males require approximately 2 gm per day of phenylalanine. Phenylalanine also is present in some artificial sweeteners.

Restricting protein intake to no more than the daily protein requirement may be beneficial for children with AKU. Such diets appear to substantially reduce the amount of benzoquinone acetic acid in the urine. In children under the age of 12, low-protein diets significantly reduce the amount of HGA in the urine, as well. However, these diets seem to have little effect on older children and young adults with AKU, and low-protein diets are difficult to maintain. When low-protein diets are prescribed, the levels of amino acids in the blood must be monitored, to assure that there is no deficiency in phenylalanine.

Ochronosis

Most treatment of AKU is directed at the diseased joints. The treatment for ochronosis is the same as for other forms of degenerative arthritis. Treatments include painkillers, physical therapy, rehabilitation, orthopedic supports, and rest. Chiropractic manipulations and exercise regimens also are utilized.

Treatment of ochronotic arthritis eventually may require hip and/or knee joint replacements with artificial materials. In older individuals, fusion of the lumbar discs of the lower spine may be necessary. Aortic valve replacement may be necessary to treat heart disease.

Future drug treatment

The National Institutes of Health are undertaking clinical research studies to better understand the clinical, biochemical, and molecular aspects of AKU. These studies are in preparation for clinical trials of a new drug to treat AKU. It is hoped that this drug will block the production and accumulation of HGA.

Prognosis

There is no cure for AKU. Essentially all individuals with AKU eventually experience arthritic symptoms, particularly arthritis of the hips, knees, and spine. The bone and joint disease may become debilitating by the sixth to eighth decades of life. Furthermore, cardiovascular involvement and ochronotic skin abnormalities are to be expected with AKU.

Despite these difficulties, individuals with AKU have normal life expectancies. Although there is an increased risk of heart attack in later life, most individuals with AKU die of causes unrelated to the disorder.

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National Heart, Lung, and Blood Institute. PO Box 30105, Bethesda, MD 20824-0105. (301) 592-8573. nhlbiinfo@rover.nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

National Institute of Child Health and Human Development (NICHD). Patient Recruitment and Public Liaison Office, Building 61, 10 Cloister Court, Bethesda, MD 20892-4754. (800) 411-1222, (301) 594-9774 (TTY), (866) 411-1010 (TTY). prpl@mail.cc.nih.gov. <http://clinicalstudies.info.nih.gov/detail/A_2000-CH-0141.html>.

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Margaret Alic, PhD

Alpha-1 antitrypsin

Definition

Alpha-1 antitrypsin is one of the most common inherited diseases in the Caucasian population. The most common symptom is lung disease (emphysema). People with alpha-1 antitrypsin may also develop liver disease and/or liver cancer. The disease is caused by a deficiency in the protein alpha-1 antitrypsin, which is why the condition is sometimes called alpha-1 antitrypsin deficiency. Other names include anti-elastase, antitrypsin, and ATT. The development of lung disease is accelerated by harmful environmental exposures, such as smoking tobacco. Alpha-1 antitrypsin is inherited. The age of onset, rate of progression, and type of symptoms vary both between and within families.

Description

The protein alpha-1 antitrypsin is a protease inhibitor, which means that it inactivates other proteins called proteases. This is an important function, as proteases themselves disable proteins. In our bodies the levels of proteases and their inhibitors are balanced so that proteases can perform their functions but not over-perform, which leads to problems.

A protease called *elastase* is the most important target of alpha-1 antitrypsin. Elastase protects the lungs against bacteria and other foreign particles. However, if the action of elastase is not kept in check, elastase destroys lung tissue. Alpha-1 antitrypsin ensures that elastase is not overactive.

Individuals with alpha-1 antitrypsin have inadequate levels of the protein alpha-1 antitrypsin. Thus, certain proteases (especially in the lungs) are overactive, which leads to emphysema and sometimes to liver disease. Alpha-1 antitrypsin is made mostly in the liver.

Some alpha-1 antitrypsin proteins are abnormal in addition to being deficient. These abnormal proteins may not move from the liver to the blood stream correctly. The build-up of the proteins in the liver may lead to liver disease. Also, the abnormal proteins may not neutralize elastase as effectively. Thus, people with alpha-1 antitrypsin have fewer proteins; those that they do have do not work as effectively.

Genetic profile

The genetics of alpha-1 antitrypsin are complicated. Scientists have identified many different forms of the **gene** that codes for the alpha-1 antitrypsin protein. This protein is often called Pi and the gene called PI, for protease inhibitor. One form of the gene, which scientists call *Z*, or PI Z, greatly reduced the amount of the active Pi protein. Because every person inherits one of each gene from his or her mother, and another copy of each gene from his or her father, everyone has two copies of every gene. People who have two copies of the PI Z gene have 85% less alpha-1 antitrypsin protein. These people have only 15% of the normal level of protein. The protein that they do have does not function as well as the normal protein. People who have one PI Z gene and one normal PI gene have about 60% of the normal level Pi protein. Other forms of the alpha-1 antitrypsin gene are associated with more or less severe deficiencies in protein.

Two other common forms of the Pi protein are called *S* and *M*. Pi M is the normal protein and PI M is the normal gene. The Pi M protein has many subtypes within the population, designated M1, M2, etc. A few abnormal alpha-1 antitrypsin genes also have unique names. The PI S gene is slightly abnormal, but not as abnormal as PI Z. Individuals with one PI S gene and one PI Z gene have approximately 38% functioning of the Pi protein (Pi SZ).

The **inheritance** of alpha-1 antitrypsin is autosomal recessive. This means that a person with alpha-1 antitrypsin has inherited one abnormal gene from each of his or her parents. The parents are most likely carriers, meaning they each have one normal gene and one abnormal gene. Two carriers have a one in four chance to have an affected child with each pregnancy. However, not all people with alpha-1 antitrypsin develop symptoms. Whether and when a person with two abnormal alpha-1

antitrypsin genes develops symptoms is related to the degree of harmful exposures, such as tobacco smoke. A person who is affected with alpha-1 antitrypsin is only at risk to have an affected child if the child's other parent is a carrier.

Although the inheritance of alpha-1 antitrypsin is autosomal recessive, the activity of the protein is equally determined by the gene inherited from either parent. For example, if a gene inherited from one parent codes for a protein with 100% activity, and the gene inherited from the other parent codes for a protein with 0% activity, the offspring would have 50% protein activity. The physical expression of the genes is autosomal recessive, but each gene has an equal effect on the protein activity—neither gene is dominant over the other gene. The gene for alpha-1 antitrypsin is on chromosome 14. More than 90 different forms of the gene have been identified.

Demographics

Alpha-1 antitrypsin is most common in Caucasians, especially those of Northern European descent. Alpha-1 antitrypsin is less common in populations of Asian, African, and American Indian descent. Approximately one in 2,500 Caucasians have two Z genes. These individuals account for 1% of all emphysema patients. Because people with one PI Z gene and one other deleterious PI gene may also have symptoms, the number of people at risk to have alpha-1 antitrypsin associated lung disease is greater than one in 2,500. Approximately one in 20 Caucasians has one Z gene and one normal gene. The number of Caucasians with one S gene and one normal gene is even higher. Approximately one in 1,000 Caucasians of Northern European descent have two S genes (and no normal alpha-1 antitrypsin gene).

Signs and symptoms

The main symptom of alpha-1 antitrypsin is a risk for early-onset, rapidly progressive emphysema. People with alpha-1 antitrypsin who smoke tobacco are at especially high risk. Emphysema is chronic lung disease that begins with breathlessness during exertion and progresses to shortness of breath at all times, caused by destructive changes in the lung tissue. The risk for liver disease in adults is increased, as is the risk for hepatocellular carcinoma (**liver cancer**). Some children with alpha-1 antitrypsin develop liver disease as well. Individuals with alpha-1 antitrypsin are also at risk for chronic obstructive lung disease and reactive airway disease (**asthma**). Chronic obstructive lung disease is decreased breathing capacity, which may be caused by emphysema but also has other underlying causes.

Lung disease

Approximately 60–70% of the people with two PI Z genes develop chronic lung disease. Shortness of breath with exertion may begin before the age of 40 years and progress rapidly to incapacitating emphysema. Life expectancy may be reduced by 10–15 years and is reduced further if people with two PI Z genes smoke tobacco. A portion of the people with two PI Z genes never develop chronic lung disease.

The age of onset and severity of symptoms associated with alpha-1 antitrypsin are quite variable, even within the same family. Environmental exposures significantly effect whether a person will develop symptoms. Smoking puts individuals with alpha-1 antitrypsin at much greater risk to develop emphysema. The already abnormal and deficient Pi Z protein functions 1,000 times less effectively in smokers. Researcher Ronald Crystal states, "Cigarette smoking renders an already poorly defended lung completely defenseless." People with alpha-1 antitrypsin who are not exposed to harmful environmental factors are less likely to develop emphysema. If people with two PI Z genes stop smoking before they develop lung disease, their life expectancy increases and the risk of lung disease decreases.

Individuals who have one abnormal gene with very little protein function and one gene with somewhat reduced protein function may also at risk for chronic obstructive lung disease. It is possible that people with one Z gene and one normal gene are also at risk to develop chronic lung disease if they are exposed to harmful environmental factors such as tobacco smoke. The age symptoms begin in this group would be later than that seen in people with two abnormal genes. Some researchers disagree, stating that people with PI SZ and PI MZ genes are not at significant risk for lung disease.

Liver disease

The risk of liver disease and liver cancer are increased in individuals with alpha-1 antitrypsin. Babies and children with alpha-1 antitrypsin may have abnormal liver function and inflammation. The abnormal liver function they develop is called cholestasis, which is when the liver stops secreting a digestive fluid called bile. A build-up of bile causes cholestatic jaundice (yellowing of the skin). These abnormalities sometimes progress to liver disease and liver failure, which is fatal without a liver transplant. In other babies and children, liver function returns to normal.

A small number of adults with alpha-1 antitrypsin develop liver disease, and some develop liver cancer. The age at which the liver disease begins, the rate at which it progresses, and the stage at which it is usually diagnosed

are quite variable. Adults with alpha-1 antitrypsin who had liver abnormalities as children may be at increased risk to develop liver disease or liver cancer. People with one normal PI gene and one PI Z gene may be at increased risk for liver disease.

The likelihood that a child or adult with alpha-1 antitrypsin will develop liver disease can be predicted to some degree based on which change in the gene (mutation) they have as well as their family history. The risk that a baby with two Z genes will develop significant liver disease is approximately 10%. However if a person has a family history of alpha-1 antitrypsin with liver disease, this risk may be higher. Males (both adult and children) develop liver disease more often than females. Alpha-1 antitrypsin is the most common genetic cause of liver disease in infants and children. Researchers do not know why some people with alpha-1 antitrypsin develop progressive liver disease and many others do not. The liver disease appears to be related to abnormal antitrypsin protein remaining in the liver instead of being secreted.

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Emphysema—A chronic lung disease that begins with breathlessness during exertion and progresses to shortness of breath at all times, caused by destructive changes in the lungs.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Diagnosis

Alpha-1 antitrypsin may be suspected in a newborn with cholestatic jaundice, swollen abdomen, and poor feeding. In later childhood or adulthood, fatigue, poor appetite, swelling of the abdomen and legs, or abnormal liver tests may trigger the need for testing. The diagnosis of alpha-1 antitrypsin is based on measurement of antitrypsin (Pi) in the blood. If levels of Pi are deficient, genetic studies may be performed to determine which abnormal forms of the gene are present. The Pi protein can also be studied to determine which type a person has. Prenatal diagnosis is available, however, it is recommended that parental genetic studies precede prenatal testing to ensure accurate interpretation of results.

Levels of antitrypsin protein in the blood may be normal in individuals who have one PI Z gene and one normal gene, and in individuals who have one PI S gene and one PI Z gene. Studying the Pi protein will more accurately diagnose these individuals.

Lung disease in people with alpha-1 antitrypsin is diagnosed by the same methods used to diagnose lung disease in people who do not have alpha-1 antitrypsin. These studies include breathing tests such as total lung capacity and pulmonary function tests. Total lung capacity is measured with a device called a spirometer. Pulmonary function tests measure oxygen/carbon dioxide exchange by determining the amount of air exhaled, the time to exhale, and the efficiency of oxygen transport. X rays and other studies may also be performed.

Liver disease in children and adults with alpha-1 antitrypsin is diagnosed by the same methods used to diagnose liver disease in people who do not have alpha-1 antitrypsin. Liver function studies include tests measuring two liver proteins called serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). SGOT is sometimes called aspartate transaminase (AST), and SGPT is sometimes called alanine aminotransferase (ALT). Studies may also be performed looking for deposits within the cells of the liver called inclusions.

Once the diagnosis of alpha-1 antitrypsin has been made, it is important to share this information with relatives related by blood, especially parents and children. These relatives may also have alpha-1 antitrypsin. If they know that they have it before they develop lung disease, they can take preventative measures such as avoiding exposure to smoke and other lung toxins. Some organizations have recommended that individuals with asthma be tested for alpha-1 antitrypsin.

Treatment and management

Although alpha-1 antitrypsin cannot be prevented, many of the condition's consequences can be prevented. People with alpha-1 antitrypsin should not smoke cigarettes and should not be exposed to smoke or other lung

irritants. Respiratory infections should be treated promptly because they increase the level of harmful elastase in the lungs. Some doctors recommend avoiding alcohol and oxidants; keeping hepatitis A and B vaccinations, pneumococcal vaccinations, and influenza shots up-to-date; and preventing hepatitis C exposure.

Protein augmentation

Treatment is available if individuals with alpha-1 antitrypsin develop lung disease. Infusion of alpha-1 antitrypsin protein into the bloodstream may halt or slow progression of respiratory problems. The protein is put into a blood vein weekly, biweekly, or monthly. Treatment with the replacement protein may not be effective if tissue damage to the lungs is severe. This is often called augmentation therapy. This therapy is safe and people who receive it have few adverse reactions. However, some researchers are not convinced that it is an effective treatment.

People with alpha-1 antitrypsin who have diminished lung air capacity but no other symptoms may be given prophylactic replacement antitrypsin infusions. In the year 2000, the success of prophylactic treatment has not been confirmed. The controversy over augmentation therapy may be resolved in 2001. A task force currently addressing this issue and others is scheduled to publish treatment and standard of care recommendations at that time.

Treatments in development

People who have two abnormal PI genes have reason to be hopeful that effective treatments may be available by 2010. The Pi protein may be available in an inhaled form in the first few years of the new millennium. Biotechnology based treatments such as aerosols that deliver the normal gene to lung tissue are being studied. Lung transplant may be an option in the future.

Liver disease treatments

Some doctors advocate regular monitoring of liver function in elderly patients with alpha-1 antitrypsin. In most people with alpha-1 antitrypsin, an initial liver function evaluation will be performed but it will only be repeated if the person has symptoms. Augmentation therapy (replacing the protein in the blood) does not effectively treat the liver disease. In 2001, **gene therapy** for liver disease is not possible.

The treatment for children with alpha-1 antitrypsin who develop liver disease is a liver transplant. Alpha-1 antitrypsin is a common reason for liver transplant in the pediatric population. If the new liver is from a donor with normal alpha-1 antitrypsin, the new liver will have normal, functional protein after the transplant.

Prognosis

Individuals with alpha-1 antitrypsin who have never smoked nor been exposed to other respiratory irritants have the best prognosis. They may never develop lung disease. If they do develop lung disease, the age of onset is usually later than that of smokers—10 or more years later. Prognosis is improved if people with alpha-1 antitrypsin stop smoking before the onset of lung disease.

The lung disease people with alpha-1 antitrypsin develop typically progresses rapidly. Affected individuals may progress from decreased respiration during exertion to incapacitation in five years. Smoking cessation and prompt treatment are critical. Prompt treatment with replacement protein improves prognosis. Some scientists recommend delaying treatment until the affected person has quit smoking.

Prognosis of infants with liver disease is poor. If a donor is found and transplant successful, the new liver has the alpha-1 antitrypsin gene of the donor. Therefore, if the liver transplant is successful the prognosis related to alpha-1 antitrypsin is very good.

A great deal of research is done on the prevention and cure of alpha-1 antitrypsin. In 1996, the World Health Organization sponsored a meeting of experts who study the disease. The experts outlined specific topics to be researched, which included studying treatments. In 1997, 12 countries with registries of alpha-1 antitrypsin patients formed an international registry. This will make it easier for researchers to complete studies involving large numbers of patients, which are absolutely necessary to answer research questions (especially treatment questions). Pharmaceutical companies are also studying new treatment options. Researchers are hopeful about new treatments that may become available. Even with new medicines, the most important treatment for alpha-1 antitrypsin will probably be prevention.

Resources

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Crystal, Ronald G., ed. *Alpha 1-Antitrypsin Deficiency.* Lung Biology in Health & Disease Series, vol. 88. New York: Marcel Dekker, Inc., 1995

ORGANIZATIONS

Alpha 1 National Association. 8120 Penn Ave. South, Suite 549, Minneapolis, MN 55431. (612) 703-9979 or (800) 521-3025. julie@alpha1.org. <http://www.alpha1.org>.

Alpha One Foundation. 2937 SW 27th Ave., Suite 302, Miami, FL 33133. (305) 567-9888 or (877) 228-7321. mserven @alphaone.org. <http://www.alphaone.org>.

Alpha to Alpha. RR#5 Box 859, Warsaw, MO 65355. (660) 438-3045. <http://www.alpha2alpha.org>.

AlphaNet. (800) 557-2638. <http://www.alphanet.org>.

American Liver Foundation. 75 Maiden Lane, Suite 603, New York, NY 10038. (800) 465-4837 or (888) 443-7222. <http://www.liverfoundation.org>.

American Lung Association. 1740 Broadway, New York, NY 10019-4374. (212) 315-8700 or (800) 586-4872. <http://www.lungusa.org>.

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Michelle Queneau Bosworth, MS, CGC

Alzheimer disease

Definition

Alzheimer disease is a form of **dementia** caused by the destruction of brain cells. Dementia is the loss, usually progressive, of cognitive and intellectual functions. Alzheimer type dementia can be characterized by initial short-term memory loss, which eventually becomes more severe and finally incapacitating.

Diagnosis before death is based upon clinical findings of unexplained slowly progressive dementia and neuroimaging studies that show gross cerebral cortex atrophy (changes in the structure of the brain, usually in the form of shrinkage). Neuroimaging refers to the use of positron emission tomography (PET), magnetic resonance imaging (MRI), or computed topography (CT) scans. These are special types of pictures that allow the brain or other internal body structures to be visualized. Professor Alois Alzheimer of Germany first described the condition is 1907.

Description

Sporadic Alzheimer's accounts for over 75% of cases of Alzheimer disease. Sporadic Alzheimer patients do not have a family history of Alzheimer disease and may develop the disease at any time during their adult life. A family history is positive for Alzheimer's if three or more generations of a family exhibit signs of the disease. Patients are diagnosed with sporadic Alzheimer disease after all other causes of dementia are excluded.

KEY TERMS

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

Plaques—Abnormally deposited proteins that interfere with normal cell growth and functioning and usually progresses to cell death.

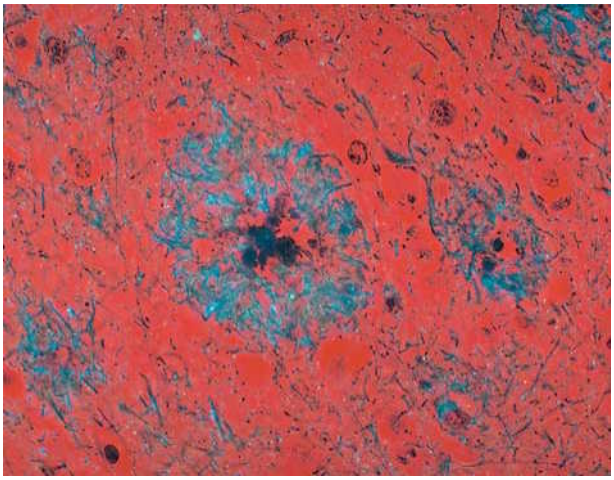
There are five common causes of dementia. If a patient has a history of strokes (blood clot in the brain) and stepwise destruction of mental capacities, multi-infarct vascular (arteries) dementia must be considered. Diffuse white matter disease is another form of vascular dementia that must be excluded as a possible cause of dementia. Diagnosis of diffuse white matter disease is made by MRI, which shows generalized death of large parts of the brain.

Parkinson disease is a brain nerve disease, which causes abnormalities in movement and functioning. Parkinson's can be excluded by clinical presentation because most patients experience tremors and rigidity of arms and legs.

Alcoholism can also lead to dementia because patients who ingest increased quantities of alcohol over many years may have digestive problems that lead to nutritional deficiencies. These patients may experience malnutrition and possible lack of absorption of vitamins such as thiamine (B_1), cobalamin (B_{12}) and niacin (nicotinic acid). These vitamins are essential for proper function of the body and brain. Continued use of certain drugs or medications such as tranquilizers, sedatives, and pain relievers can also cause dementia. It is important to note that alcoholism and over use of medications are potentially reversible causes of dementia.

The less common causes of dementia that must be excluded as possible contributors are endocrine abnormalities (abnormalities in the hormones of the body). Thyroid dysfunction is the leading abnormality. The thyroid gland produces hormones that are essential for the basic functions of the body such as growth and metabolism. Abnormalities of the thyroid can be diagnosed by a blood test. Chronic infections, trauma or injury to the brain, tumors of the brain, psychiatric abnormalities such as **depression**, and degenerative disorders should also be ruled out as causes of dementia. (A degenerative disorder is a condition that causes a decrease in mental or physical processes).

Familial Alzheimer disease accounts for approximately twenty-five percent of cases of Alzheimer disease.



Diseased brain tissue from a patient with Alzheimer disease showing senile plaques, seen as darker spots surrounded by lighter haloes, center and center right, located in gray matter of the brain. *(Photo Researchers, Inc.)*

Familial Alzheimer's is diagnosed if other causes of dementia are ruled out and if there is a family history of the disease. Familial Alzheimer's is further subdivided into early and late onset. Early onset indicates that the patients exhibit unexplained dementia before the age of 65. Late onset refers to the development of unexplained dementia after the age of 65. Late onset is two to four times more prevalent than early onset.

Alzheimer disease associated with **Down syndrome** accounts for the remaining less than one percent of Alzheimer cases. Studies have shown that Down syndrome patients over the age of forty all develop the brain cell changes that are characteristic of Alzheimer disease. Because the function of the brain is already impaired in a Down syndrome patient it is difficult to determine if changes in outward actions are related to Down syndrome or to the progression of Alzheimer disease.

Genetic profile

The **gene** that causes sporadic Alzheimer disease has not been identified. Currently sporadic Alzheimer's is believed to be the result of a combination of multiple environmental influences and genetic mutations. This view is supported by research involving identical twins. Both twins develop Alzheimer disease only one third of the time. This supports the view that something besides genetic predisposition has an affect on whether sporadic Alzheimer disease develops. Females who have the Apolipoprotein E (ApoE) gene on chromosome 19 have been shown in certain cases to have an increased risk for developing sporadic Alzheimer disease. A mutation in the ApoE gene has been shown to cause an increase in the amount of A-beta Amyloid. A-beta Amyloid is a protein that is deposited in increased amounts in the brain of patients with Alzheimer's. Deposits of this protein in the brain are thought to interfere with another protein, which maintains nerve cell shape. A genetic test is available that detects the defect in ApoE.

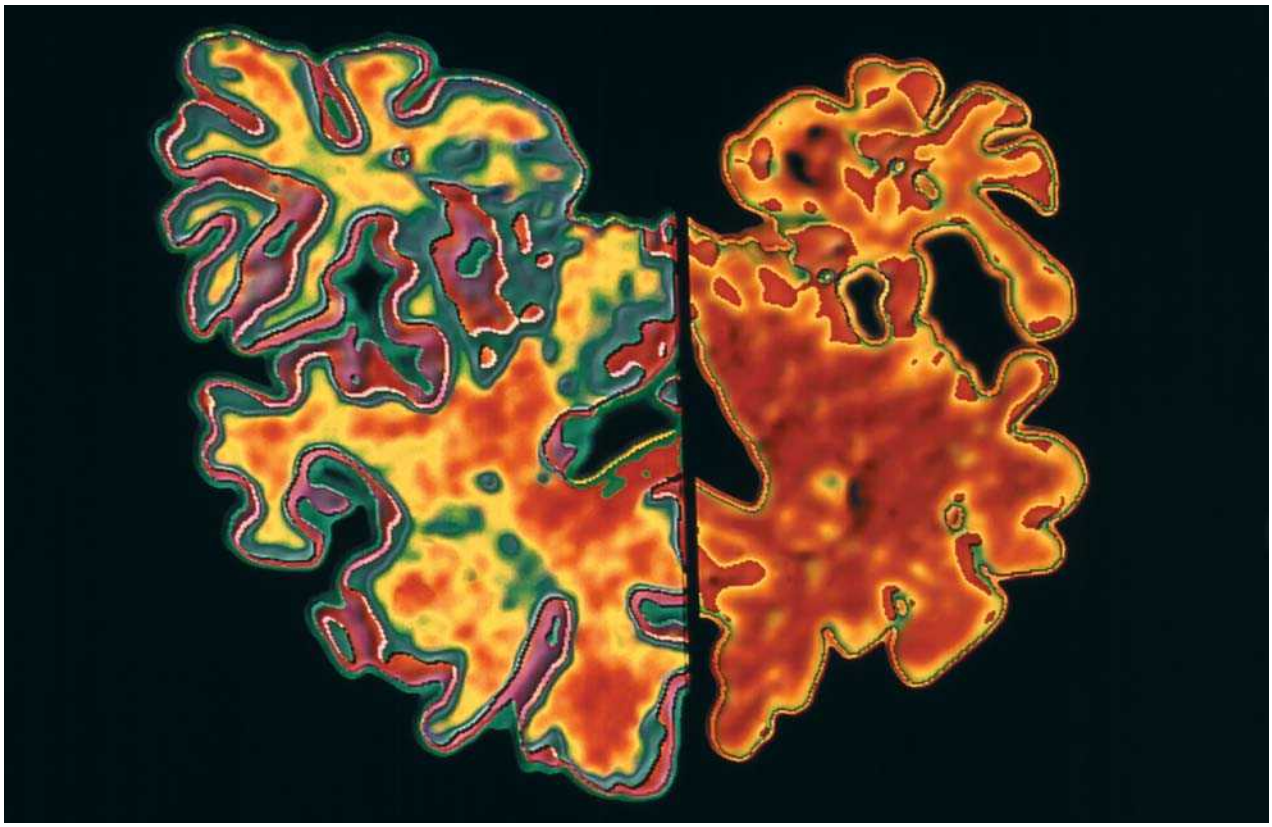
Familial early onset Alzheimer's has been associated with several genetic mutations. Identification of several genetic mutations has led to the further subdivision of early onset disease into three categories. AD3 refers to a genetic defect in the presenilin 1 (PSEN1) gene located on chromosome 14. AD1 is a genetic defect in the Amyloid precursor protein (APP) gene located on chromosome 21. AD4 is a genetic defect in the presenilin 2 (PSEN2) gene located on chromosome 1. The three genetic mutations account for approximately 50% of early onset familial Alzheimer's. All three of these genetic mutations result in an increased amount of A-beta Amyloid. AD3 has a genetic test currently available that has been shown to detect the AD3 mutation with 20-27% accuracy. Genetic tests for AD1 and AD4 are in the research stage of development. Familial early onset Alzheimer's is most commonly transmitted by autosomal dominant **inheritance**. Autosomal dominant means that either affected parent has a 50% chance of transmitting the disease to their male or female children.

The gene for familial late onset Alzheimer disease (AD2) has not been identified. An association has also been found with mutations in ApoE.

The normal person has two copies (one from each parent) of each of the 22 **chromosomes**. Down syndrome patients have three copies of chromosome number 21. Brain changes that are similar to those that occur in sporadic and familial Alzheimer's patients are attributed to the gene defect in chromosome 21. Down syndrome patients also experience additional brain related changes that are similar to Alzheimer's patients, but the gene defect for these changes has not been determined.

Demographics

Alzheimer disease is the most common form of dementia in North America and Europe. Alzheimer disease occurs most often in people over age 60 and affects 5% of individuals over the age of 70. It is estimated that four million people in the United States are afflicted with Alzheimer disease and this number is expected to increase as the estimated life expectancy of Americans increases. Females may be at greater risk than males.



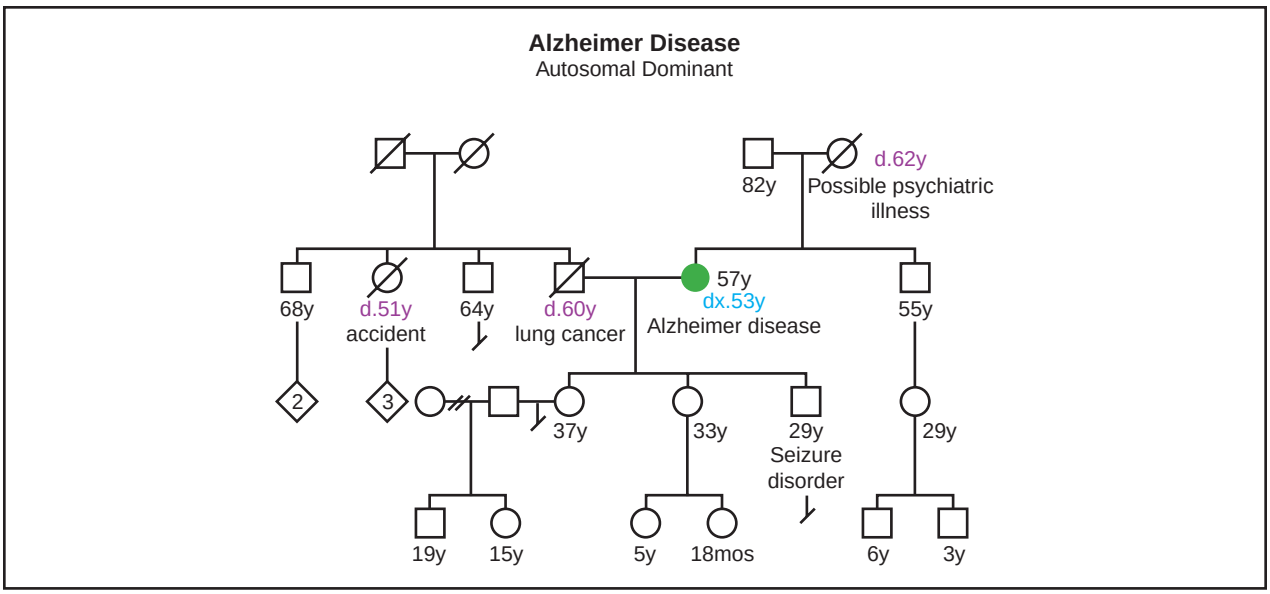
Computer graphic compairing the brain affected by Alzheimer disease (right) to that of a normal brain (left). Due to degeneration and death of nerve cells, the affected brain is considerably smaller. *(Photo Researchers, Inc.)*

Signs and symptoms

Patients with Alzheimer disease progress at different rates. Progression of memory loss will vary from person to person. Impaired memory will eventually begin to interfere with daily activities. Patients may not be aware that they are experiencing failure in memory, a condition referred to as agnosognosia. Other patients are keenly aware of their memory loss and may become anxious and frustrated. Early phase manifestations of Alzheimer's often include anxiety and frustration. Patients may also begin to experience disorientation to place and become confused by changes of environment.

During the middle phase of the disease, an individual may not be able to be left unattended. The patient can become easily confused and lost. Difficulty in many aspects of language appears at this time. Patients experience problems with comprehension and remembering the names of things in their environment. Their speech may not flow smoothly when they talk and they may experience difficulties repeating previously explained information. Simple mathematical calculations or performing tasks such as dressing or preparing a meal at the correct time may also become impaired. Because there is individual variation in the progression of the disease, some patients may still be able to continue routine behavior and engage in a generalized type of conversation during this phase of the disease. A small number of patients may experience difficulties seeing. Changes in vision are frequently denied and only confirmed by autopsy results after death that indicate destruction in the areas of the brain, which process visual images.

If a patient remains able to get out of bed in the late phase of Alzheimer disease they may wander aimlessly. Wandering must be monitored at night because sleeping patterns may become altered. Walking may become difficult in the late phase of Alzheimer's because some patients experience stiffening of muscles that causes their movement to be awkward and slow. Patients will require constant supervision. Rationalizing with patients becomes very difficult at this time because they experience severe mental changes. They are often unable to reason or demonstrate appropriate judgment. Patients may become uninhibited and confrontational. They may experience delusions, which are false beliefs despite ample evidence to the contrary. This can be manifested in ways



(Gale Group)

such as not recognizing a family member or accusing a spouse of infidelity. A patient with Alzheimer's may also perceive objects in their environment that do not actually exist.

In the final stage of Alzheimer's, patients may need assistance with the simplest activities of daily living such as feeding ones self and changing clothes. A majority of patients will be bedridden and their muscles will be stiff to the point where they cannot bend. Many are unable to talk and have lost total control of their bowel and urinary functions. Abnormal jerking movements of the body may occur for no reason. Touching a patient or certain noises may precipitate these abnormal body movements. When reflexes such as the knee (tapping of the leg below the knee) are tested, there are frequently exaggerated responses. Some patients additionally experience whole body contractions, known as a generalized seizure.

Diagnosis

Diagnosis is established based upon exclusion of other possible causes for dementia. Obtaining an accurate medical history is essential in this process. An accurate family history including a history of family members who have had Alzheimer disease and age of onset must be obtained.

The earliest changes in the structure of the brain are seen using PET scans. MRI and CT scans are most useful in the early phase of the disease to exclude other brain abnormalities that may be causing dementia. As the disease progresses, use of MRI and CT scans will show changes in the structure of the brain tissue that indicate brain cell death. As of 2000, studies indicate that MRI is statistically accurate in predicting who may or may not develop Alzheimer disease in the future.

Diagnosis is not confirmed unless an autopsy is preformed after death. The brain of a patient with Alzheimer's will have A-beta amyloid neuritic plaques (senile plaques) and intraneuronal neurofibrillary tangles. These are changes in specific proteins and nerve structures of the brain that occur normally as an individual ages but are greatly increased in patients with Alzheimer disease. These brain changes are similar in sporadic, familial early onset, familial late onset, and patients with Down syndrome related Alzheimer disease. It is also noted that the longer the disease process for an individual lasts, the smaller their brain is upon death.

Treatment and management

Because the course of Alzheimer disease has great individual variation, treatment is aimed at being supportive of both patient and caretakers. Neurological and behavioral problems are treated as needed.

Alzheimer disease is associated with decreased levels of specific chemicals called acetylcholine and norepinephrine. Acetylcholine and norepinephrine are chemicals important in many processes in the body including digestion, blood vessel dilation and constriction (usually refers to blood vessel diameter becoming smaller), and regulation of heart beat. Acetylcholinesterase is an enzyme in the body that breaks down acetyl-

choline. One class of drugs is currently available in the United States that inhibits this process. Use of these medications has been shown to increase levels of acetylcholine in the brain, resulting in improved brain function in patients who are in the early phase of the disease.

Many early phase patients with Alzheimer's experience depression. Antidepressants such as selective serotonin reuptake inhibitors are the most commonly used class of drugs for treatment of depression. This class of drugs helps to stabilize certain chemicals in the brain. Seizures, anxiety, agitation, defiant behavior, inability to sleep, and hallucinations are treated on an as needed basis. Patient and caregiver should establish a relationship with a primary care provider. Nutritional intake needs monitoring since patients will eventually lose capabilities required for maintaining their diet and also because advancing age itself results in decreased appetite. The home environment must be made as safe as possible and the patient should be monitored closely for the point at which they are no longer able to drive safely. Because disorientation is frequently experienced, it is important to maintain the patient within a stable and familiar environment.

Caregivers need to remain calm and offer reassurance. Community organizations that offer help should be sought. Support groups for caretakers offer places to express feeling and help in anticipating future problems. The patient must be monitored closely during the times when they are unable to determine their own care. Financial assets and plans for the ongoing management of the disease should be addressed before this advanced stage is reached. Nursing home placement is an option for patients with Alzheimer disease without caretakers or for patients who become unmanageable in the home environment.

Individuals who have a history of familial Alzheimer disease in their family should consider **genetic counseling**. Genetic counseling will help to clarify possible risk factors and determine the appropriate usefulness of available genetic tests. The test for the ApoE genetic defect is not considered to be useful for prediction of sporadic Alzheimer disease in patients who do not currently have signs or symptoms of the disease.

Research treatment

Patients with Alzheimer disease have abnormal amounts of A-beta Amyloid deposited in their brain as plaques. Research involving mice in 1999 demonstrated that immunizing the animals with certain protein components of amyloid prevented the development of Alzheimer's related changes, such as plaque formation, in the brains of the mice. Immunization was also shown to slow down the brain changes in older mice. Future benefits for human use are still under investigation.

Several other drugs and combinations of drugs are currently in the beginning and end stage of research studies. Drugs affecting several different chemicals in the brain are being investigated in addition to the use of nonsteroidal anti-inflammatory drugs (drugs that reduce inflammation in the body), estrogen, and vitamin E in the prevention and alleviation of Alzheimer disease.

In April of 2001 the first use of human **gene therapy** for the treatment of Alzheimer disease was undertaken. Scientists isolated the gene of a protein found in healthy brains called nerve growth factor. This gene was transplanted into the brain of a woman with early stage Alzheimer disease. Because nerve growth factor has been shown to increase the amounts of acetylcholine in the brain, hope is that this will delay the Alzheimer's process. Further studies in this area are ongoing.

Prognosis

On average, the duration of the disease process associated with Alzheimer disease lasts eight to ten years. Death is most frequently related to malnutrition, secondary infection (infection that is not the initial medical problem) or heart disease. Malnutrition is a state when not enough calories are taken in to support the normal functions of the human body. An individual is additionally more susceptible to infections when they are malnourished. Having Alzheimer disease does not mean a patient is more likely to have heart disease. The correlation that occurs between heart disease and Alzheimer disease is the fact that both increase in incidence as patients age.

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Council of Regional Networks for Genetic Services. Genetic Services Program, Wadsworth Center Labs & Research, PO Box 509, Room E299, Empire State Plaza, Albany, NY 12201-0509. (518) 474-7148. <http://www.cc.emory.edu/PEDIATRICS/corn/corn.htm>.

Laith Farid Gulli, MD
Nicole Mallory, MS

Amelia

Definition

Amelia is an extremely rare birth defect marked by the absence of one or more limbs. The term may be modified to indicate the number of legs or arms missing at birth, such as tetra-amelia for the absence of all four limbs. A related term is meromelia, which is the partial absence of a limb or limbs. Several older terms are no longer in use in international nomenclature because of their imprecision: phocomelia, peromelia, dysmelia, ectromelia, and hemimelia.

Description

The complete absence of an arm or leg in amelia occurs when the limb formation process is either prevented or interrupted very early in the developing embryo: between 24 and 36 days following fertilization. Nearly 25% of all congenital limb defects are amelia. A single limb is involved about 60% of the time and symmetrical amelia is uncommon. The likelihood for upper versus lower limb absence varies with the syndrome.

Amelia may be present as an isolated defect, but more than 50% of the time it is associated with major malformations in other organ systems. The malformations most frequently seen with amelia include cleft lip and/or palate, body wall defects, malformed head, and defects of the neural tube, kidneys, and diaphragm. Facial clefts may be accompanied by other facial anomalies such as abnormally small jaw, and missing ears or nose. The body wall defects allow internal organs to protrude through the abdomen. Head malformations may be minor to severe with a near absence of the brain. The diaphragm may be herniated or absent and one or both kidneys may be small or absent.

Other abnormalities associated with amelia include severe defects of the lungs, vertebrae, heart, internal and external genital system, and anus. There is usually a severe growth deficiency, both before and after birth, and mental retardation may be present in survivors. Benign facial tumors made up of clusters of blood vessels (hemangiomas) may be present.

Amelia was traditionally thought to be a sporadic anomaly with little risk of recurrence, or evidence of genetic origins. However, an estimated 20% of amelia cases can now be traced to probable genetic causes. These genetic conditions may be due to recessive or dominant mutations, or involve chromosomal aberrations where entire sections of **chromosomes** are deleted, duplicated, or exchanged. The best defined of these genetic diseases is known as **Roberts SC phocomelia** or Pseudothalidomide syndrome, caused by an autosomal recessive mutation of unknown location. There is a great variability of expression of the disease, even within families. Classic signs of Roberts SC phocomelia include symmetrical defects of all four limbs including amelia, severe growth deficiency, head and face (craniofacial) abnormalities such as small head and cleft lip or palate, sparse, silvery blond hair, and facial hemangiomas.

A very small group of genetically based amelia cases is referred to as "autosomal recessive tetra-amelia" which consists of an absence of all four limbs, with small or absent lungs, cleft lip or palate, malformed head and other anomalies. A similar "X-linked tetra-amelia" is highly lethal to the fetus and involves the same set of abnormalities. The abnormal **gene** for X-linked tetra-amelia is assumed to be located on the X chromosome. Very few cases have been documented for either of these inherited conditions but the defective gene seems to be more prevalent in Arab populations of the Middle East or in small isolated cultures where consanguineous relationships (intermarriage within extended families) is more common. There is disagreement as to whether these conditions represent new syndromes or are severe cases of Roberts SC phocomelia.

Amelia is associated with various other genetic syndromes. It is seen in the autosomal recessive Baller-Gerold syndrome and **Holt-Oram syndrome**, an autosomal dominant condition that sometimes involves amelia. It has been proposed that many of the new, isolated cases of amelia are due to autosomal dominant

mutations where only one copy of a defective gene on a non-sex chromosome is powerful enough to cause amelia to be displayed. Absent limbs have also been seen in chromosomal aberrations such as Trisomy 8 (three copies of chromosome 8) and a deletion of region 7q22 found on the long arm of chromosome 7.

Sporadic amelia may be the end result of various types of disturbances of limb development in the embryo. These disturbances can be vascular, mechanical, due to teratogens (substances that cause birth defects), or accompany other disease processes such as diabetes. An example of vascular disturbance would be hemorrhage in the embryo causing lack of blood and oxygen flow to surrounding tissue. The type and number of resulting defects would depend on the location of the hemorrhage and the point of embryo development when the bleed took place. Defects in limbs and the body wall tend to result from this type of disturbance.

Mechanical disruption can be seen following rupture of the amnion (the thin but tough membrane surrounding the embryo) due to infection, direct trauma such as attempted abortion or removal of IUD, or familial predisposition to rupture. Strands of the collapsed amnion and adhesions (fibrous bands which abnormally connect tissue surfaces) may entangle and amputate developing limbs and cause a variety of other defects including facial clefts.

Various teratogens are well-established causes of amelia. A well-documented historic instance was due to thalidomide use by pregnant women from 1958 to 1963. Thalidomide was used as a sedative and anti-nausea drug but was found to cause a wide array of limb deficiencies, including amelia. It is estimated to have caused 5,800 cases of malformed fetuses, mostly in Europe, but also in North America and wherever it was available worldwide. The mechanism by which thalidomide causes birth defects is still not known but may involve disruption of nerve processes. Although thalidomide is again in use today to treat certain cancers, infections, and arthritis, it should not be used by women of childbearing age.

Alcohol (ethanol) consumption by pregnant women, especially in the first trimester, has been documented by several surveys to cause limb deformities. The abnormalities range from frequent, minor defects such as shortened fingers to the much rarer amelia. It is hypothesized that alcohol interrupts the blood supply to the developing limb resulting in malformation or non-growth. Additional teratogens known to cause amelia include methotrexate, other chemotherapeutic agents and potent vasoconstrictive drugs such as epinephrine and ergotamine.

KEY TERMS

Amnion—Thin, tough membrane surrounding the embryo and containing the amniotic fluid.

Autosomal dominant mutation—An abnormal gene on one of the 22 pairs of non-sex chromosomes that will display the defect when only one copy is inherited.

Autosomal recessive mutation—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Consanguineous—Sharing a common bloodline or ancestor.

Craniofacial—Relating to or involving both the head and the face.

Hemangioma—Benign tumor made up of clusters of newly formed blood vessels.

Homeotic genes—Developmental control genes active in the embryo.

Homozygous—Having two identical copies of a gene or chromosome.

Teratogen—Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

X-linked mutation—An abnormal gene transmitted on the X chromosome.

Maternal **diabetes mellitus** (non-gestational) has long been associated with congenital anomalies, rarely including amelia. There is a two to threefold risk for congenital abnormalities in children of diabetic mothers and limb defects of various types occur in about one percent of infants of these mothers. It is thought that either abnormal maternal carbohydrate metabolism, or vascular disease resulting in decreased oxygen flow to the fetus, might play a role in causing malformations.

Genetic profile

Amelia is generally considered to be sporadic with scattered cases occurring infrequently. These rare events are presumably influenced by environmental factors, such as teratogenic drugs, maternal factors such as diabetes mellitus, and vascular accidents in the uterus. The role of genetics in causing this condition is still undetermined but two large epidemiological studies estimate that nearly 20% of amelia cases are of genetic origin.

Mutations in more than one gene with different modes of transmission can lead to this severe limb deficiency.

Recurrence of amelia within families is the exception. When this occurs, it is most often associated with other malformations in autosomally recessive syndromes such as Roberts SC phocomelia, autosomal recessive amelia, and X-linked amelia. Roberts SC phocomelia has a clearly identifiable genetic abnormality that can be seen during chromosome analysis. The abnormality is called either Premature Centromeric Separation (PCS) or Heterochromatin Repulsion (HR). The darkly staining heterochromatin of the chromosome can be seen puffing and splitting. The PCS test is positive in about 80% of patients with Roberts SC phocomelia.

Demographics

The rarity of amelia makes the study of it on a population level speculative. A few large-scale studies pooling decades of information from malformation registries in several countries do provide preliminary data. Amelia has an incidence of 11-15 cases per million live births and 790 cases per million stillbirths. The condition is probably under reported due to lack of documentation of some miscarriages, stillbirths, and neonatal deaths.

There is no significant difference between number of males and females affected except in the select, extremely rare cases of X-linked amelia, which are all male. Only men would be affected since the abnormal gene is inherited on the X chromosome and men only receive one copy of an X chromosome. Since females inherit two copies of the X chromosome, the normal copy of the gene on the second X chromosome can usually mask the more severe complications that would result if only the abnormal gene was expressed.

The disorder occurs worldwide and there are no geographic clusters except for two. Amelia resulting from the use of thalidomide occurred primarily in Europe and other areas where the drug was available. Autosomal recessive and X-linked amelia has mostly occurred in Arabic and Turkish families. This suggests ethnic differences for an abnormal recessive gene but is based on less than 20 cases. Such a recessive gene is likely to be homozygous (meaning two copies of the abnormal gene need to be inherited for amelia to result), and thus expressed in malformation more often in any culture that tends to be isolated and has more intermarriage from a limited **gene pool**.

Signs and symptoms

Prior to clinical observation of absent limbs, certain signs in the pregnant mother may indicate a greater likelihood of amelia. Abnormal vaginal bleeding, diabetes mellitus, and toxemia (disturbed metabolism during pregnancy characterized by high blood pressure, swelling and protein in the urine) are all associated with amelia in the fetus. Alpha fetoprotein is a protein normally produced by the liver of the fetus which then circulates in the mother's blood. An increased alpha fetoprotein in the maternal blood may indicate neural tube defects that can accompany limb defects. Besides seeing missing limbs by ultrasound, signs in the fetus accompanying amelia include breech and other non-cephalic presentations at birth (where the baby is not in the normal head-first, face-down delivery positon), an increased frequency of only a single artery in the umbilical cord, low placental weight and extremely low birth weight, not accounted for by the lack of limbs. The average birth weight for an infant with amelia is less than the third percentile for its age.

Diagnosis

Detection of an absent limb is generally simple. Clinical observation of the missing limb is either made at birth or prenatally by ultrasonography. However, more than 50% of amelia cases are accompanied by malformations of other organ systems, and in these cases, determination of a specific syndrome can be difficult. Defects overlap greatly between conditions. A family history including a pedigree chart to map other affected family members can be very helpful in detecting genetic causes. A prenatal history should include determination of maternal exposure to alcohol, thalidomide, and other teratogenic drugs. Maternal diabetes mellitus should be considered a risk factor for congenital abnormalities.

Roberts SC phocomelia must be differentiated from other autosomal recessive or X-linked amelias. **Genetic testing** for PCS should be performed on cells from amniotic fluid. Darkly staining heterochromatin of the chromosome puffs out abnormally and splits in a positive test. The PCS test will be positive in nearly 80% of Roberts SC phocomelia cases but negative in the other syndromes. A positive PCS test along with some of the signs listed above, is diagnostic for Roberts SC phocomelia. Further chromosome studies should be done to detect gross chromosomal aberrations such as deletions or Trisomy 8.

Treatment and management

Preventive measures to avoid serious limb defects such as amelia include avoidance of thalidomide and other teratogens in women of childbearing years, avoidance of alcohol during pregnancy, and comprehensive

management of diabetes mellitus throughout pregnancy. A prenatal ultrasound that detects an absence of limbs can be followed by chromosome analysis and **genetic counseling** to make informed decisions regarding termination.

Children with amelia can be fitted with a prosthesis to substitute for the missing limb. Surgery is often performed to repair craniofacial defects. Minimal to full time care may be needed depending on the degree of mental retardation.

Prognosis

When amelia occurs as an isolated abnormality, prognosis is good. However, when amelia is combined with multiple other defects, the prognosis is grim. Abnormalities accompanying amelia may include cleft lip and/or palate, body wall defects, malformed head, and abnormalities of the neural tube, kidneys, and diaphragm. Many infants die prior to birth. Sixty percent of newborns die within the first year, with half not surviving the first day. Mild cases of Roberts SC phocomelia are likely to survive past the first few years and reach adulthood. Infants with severe growth deficiency and craniofacial defects from Roberts SC phocomelia and amelia do not live past the first few months.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Marianne F. O'Connor, MT (ASCP), MPH

Amniocentesis

Definition

Amniocentesis is an optional procedure offered to women during pregnancy in order to obtain more information about a developing fetus. A doctor uses a thin, hollow needle to remove a small sample of amniotic fluid from around the developing baby. An ultrasound exam is usually performed at the same time to help guide the needle. The fluid sample is used to look for specific types of medical problems in the fetus. Tests done on amniotic fluid obtained by amniocentesis cannot evaluate the fetus for every potential kind of problem. The information it does provide, however, is very accurate. The procedure is associated with a slightly increased chance for pregnancy loss. Women who undergo amniocentesis typically do so either to obtain reassurance about fetal well-being or, if the results are abnormal, to plan for the remainder of their prenatal care.

Description

Amniocentesis is the most common invasive prenatal diagnosis technique offered to pregnant women. A sample of amniotic fluid can be used to detect **chromosomal abnormalities** in a fetus, certain other types of congenital disorders, or other medical indicators. Its safety and accuracy are well-established, and it is generally considered the "gold standard" by which other prenatal diagnosis techniques are measured.

The word amniocentesis is derived from the Greek words, *amnion* and *kentesis*, meaning "lamb" and "puncture," respectively. In order to perform the procedure, a doctor inserts a thin needle into the mother's uterus and the amniotic sac. A continuous ultrasound evaluation is typically used so that the doctor can avoid touching both the baby and the umbilical cord with the needle. The amniotic sac is made up of two membranes: the inner *amnion* and the outer *chorion*. The amnion and chorion both develop from the fertilized egg. They are initially separate but begin to fuse early in pregnancy. This fusion is usually completed by approximately the fourteenth to fifteenth week of pregnancy.

Amniocentesis is usually performed in the second trimester, usually during weeks 16–18 (mid-trimester). The amniotic sac holds the fetus suspended within the amniotic fluid, an almost colorless fluid that protects the

fetus from harm, helps maintain a consistent temperature, and prevents the fetus, or parts of it, from becoming attached to the amnion. The amniotic fluid is produced and absorbed by the fetus throughout pregnancy. Fetal cells, primarily derived from the skin, digestive system, and urinary tract, are suspended within the fluid. A smaller number of cells from the amnion and placenta are also present. Finally, the fetus produces a number of different chemical substances that also pass into the amniotic fluid. These substances may be used, in some higher-risk pregnancies, either to assess fetal lung maturity or to determine if the fetus has a viral infection. In the second trimester of pregnancy, one particular protein, called *alpha-fetoprotein*, is commonly used to screen for certain structural birth defects.

It is possible to perform amniocentesis in a twin pregnancy. Amniocentesis in some higher-order pregnancies, such as triplets, has also been reported. In a multiple pregnancy, it is important to ensure that a separate sample of amniotic fluid is obtained from each fetus. To accomplish this, a doctor injects a small amount of harmless blue dye into the amniotic sac of the first baby after a sample has been withdrawn. The dye will temporarily tinge the fluid blue-green. A second needle is inserted into the next amniotic sac with ultrasound guidance. If the fluid withdrawn is pale yellow, a sample from the next fetus has been successfully obtained. In the case of monoamniotic (in one amniotic sac) twins or triplets, the genetic material in each fetus is identical, so only one sample needs to be taken.

Indications for amniocentesis

Amniocentesis has been considered a standard of obstetrical care since the 1970s. It is not, however, offered to all pregnant women. The American College of Obstetricians and Gynecologists (ACOG) recommends that amniocentesis be offered to all expectant mothers age 35 and older. This age cut-off has been selected because advancing maternal age is associated with an increasing risk of having a baby with a numerical chromosome abnormality. At age 35, this risk is approximately equivalent to the risk of pregnancy loss associated with amniocentesis.

A person normally has a total of 46 **chromosomes** in each cell of his or her body, with the exception of sperm or egg cells, which each have only 23. As women get older, there is an increased risk of producing an egg cell with an extra chromosome. This leads to an egg cell with 24 chromosomes rather than the normal 23. Pregnancies with an abnormal number of chromosomes are referred to as aneuploid. Aneuploidy results in a conceptus (product of conception) with either too much or too little genetic material. This, in turn, leads to abnormal development. Common effects of aneuploidy include an increased risk for pregnancy loss or, in live borns, for mental retardation and physical abnormalities.

Down syndrome is the most common form of aneuploidy in live born infants, occurring in approximately one in 800 births, regardless of maternal age. In women who are 35 years old, the risk of having a child with Down syndrome is higher, or roughly one in 385 at delivery. It is important to realize that Down syndrome is not the only chromosome abnormality that may occur. Other numerical abnormalities are possible, yielding genetic conditions that may be either more or less severe than Down syndrome. Thus, a woman is often given a risk, based solely on her age, of having a child with *any* type of chromosome abnormality. At age 35, this total risk is approximately one in 200. By age 40, this risk has increased to one in 65, and, at age 45, this risk is one in 20. These numbers reflect the risk at the time of delivery.

Women younger than 35 years may also have children with chromosomal or other **genetic disorders**. Therefore, other indications for amniocentesis or other forms of prenatal diagnosis include a family history of, or a previous child with, a known genetic condition; abnormal prenatal screening results, such as ultrasound or a blood test; or one parent with a previously identified structural chromosome rearrangement. All of the above may make it more likely for a couple to have a child with a genetic condition.

Side effects

Women who have had an amniocentesis often describe it as uncomfortable, involving some mild pressure or pain as the needle is inserted. Fewer women describe it as extremely painful. A local anesthetic may be used to numb the upper layer of the mother's skin prior to testing. This medicine has no effect on the fetus, but may help the mother feel more comfortable during the procedure. An experienced physician can, on average, perform amniocentesis in approximately one to two minutes.

Common complaints after amniocentesis include mild abdominal tenderness at the site of needle insertion or mild cramping. These usually go away within one to two days. More serious complications are significantly less common but include leakage of amniotic fluid, vaginal bleeding, or uterine infection. These complications are estimated to occur in fewer than 1% of pregnancies. In some women, complications after amniocentesis may lead to a miscarriage, or loss of the pregnancy. A woman's background risk of having a miscarriage, without amniocentesis, is approximately 2–3% in her second trimester. When performed by an experienced physician or technician, the risk for an amniocentesis-related preg-

KEY TERMS

Amnion—Thin, tough membrane surrounding the embryo and containing the amniotic fluid.

Anesthetic—Drug used to temporarily cause loss of sensation in an area of the body. An anesthetic may either be general, associated with a loss of consciousness, or local, affecting one area only without loss of consciousness. Anesthetics are administered either via inhalation or needle injection.

Chorion—The outer membrane of the amniotic sac. Chorionic villi develop from its outer surface early in pregnancy. The villi establish a physical connection with the wall of the uterus and eventually develop into the placenta.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Conceptus—The products of conception, or the union of a sperm and egg cell at fertilization.

Cystic fibrosis—A respiratory disease characterized by chronic lung disease, pancreatic insufficiency and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encode a transmembrane receptor.

Down syndrome—A genetic condition characterized by moderate to severe mental retardation, a characteristic facial appearance, and, in some individuals, abnormalities of some internal organs. Down syndrome is always caused by an extra copy of chromosome 21, or three rather than the normal two. For this reason, Down syndrome is also known as *trisomy 21*.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term embryo is used prior to the third month.

Fibroid—A non-cancerous tumor of connective tissue made of elongated, thread-like structures, or fibers, which usually grow slowly and are contained within an irregular shape. Fibroids are firm in consistency but may become painful if they start to break down or apply pressure to areas within the body. They frequently occur in the uterus and are generally left alone unless growing rapidly or causing other problems. Surgery is needed to remove fibroids.

Sickle cell anemia—A chronic, inherited blood disorder characterized by sickle-shaped red blood cells. It occurs primarily in people of African descent, and produces symptoms including episodic pain in the joints, fever, leg ulcers, and jaundice.

Tay-Sachs disease—An inherited biochemical disease caused by lack of a specific enzyme in the body. In classical Tay-Sachs disease, previously normal children become blind and mentally handicapped, develop seizures, and decline rapidly. Death often occurs between the ages of three and five years. Tay-Sachs disease is common among individuals of eastern European Jewish background but has been reported in other ethnic groups.

Trimester—A three-month period. Human pregnancies are normally divided into three trimesters: first (conception to week 12), second (week 13 to week 24), and third (week 25 until delivery).

Uterus—A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertil-

nancy loss is estimated to be an additional 0.25%–0.50%, or roughly one in every 200–400 pregnancies.

Much attention is often paid to the physical side effects of amniocentesis. However, it is important to also emphasize some of the emotional side effects of amniocentesis. Many of these are applicable to other forms of prenatal diagnosis.

The offer of prenatal testing is associated with increased anxiety. This appears to be true whether a woman knew prenatal testing would be offered to her during the pregnancy or if it comes about unexpectedly, as is usually the case following abnormal screening results. Women to whom genetic amniocentesis is presented must consider the perceived benefits of testing, such as the reassurance that comes when results are normal, and compare them to the possible risks. Potential risks include not only complications after testing but also learning of having a child with a serious disability or chronic medical condition. The nature of the child's possible diagnosis is also important. For example, could it lead to an early death, be more subtle and cause few out-

ward signs of a problem, or be somewhere in between? There are few treatments available to correct the hundreds of genetic disorders so far described. Couples may consider whether or not they would consider early termination of the pregnancy if a serious abnormality were detected. The definition of "serious" is often a matter of personal opinion. A couple's value system and family history, including that of other pregnancies and their outcomes, all influence their decision regarding amniocentesis. Ideally, a woman and her partner will have discussed at least some of these issues with each other and with either the woman's doctor or a genetic counselor prior to testing. The choice to have amniocentesis depends on many factors and should remain a personal decision.

Results

Genetic testing is available on amniotic fluid obtained by amniocentesis. The most common test result is a complete analysis of the fetal chromosomes. After a sample of amniotic fluid is obtained, the genetic laboratory isolates the cells, referred to as amniocytes, out of the fluid. The cells are placed into two or more containers filled with liquid nutrients, establishing different cultures in which the cells will continue to grow. The cells are cultured anywhere between one to two weeks before the actual analysis begins. This is done in order to synchronize the growth of the cells within a culture. Also, chromosomes are only microscopically visible at a specific point during cell division.

Once there appears to be an adequate number of cells to study, the cultures are harvested. Harvesting prevents additional cell growth and stops the cells at whatever point they were in their division process. A careful study of the total number and structure of the chromosomes within the cells may now be performed. Typically, chromosome results are available within 7–14 days after amniocentesis. Results may be delayed by slow-growing cultures. This rarely reflects an abnormal result but does extend the time until final results are ready.

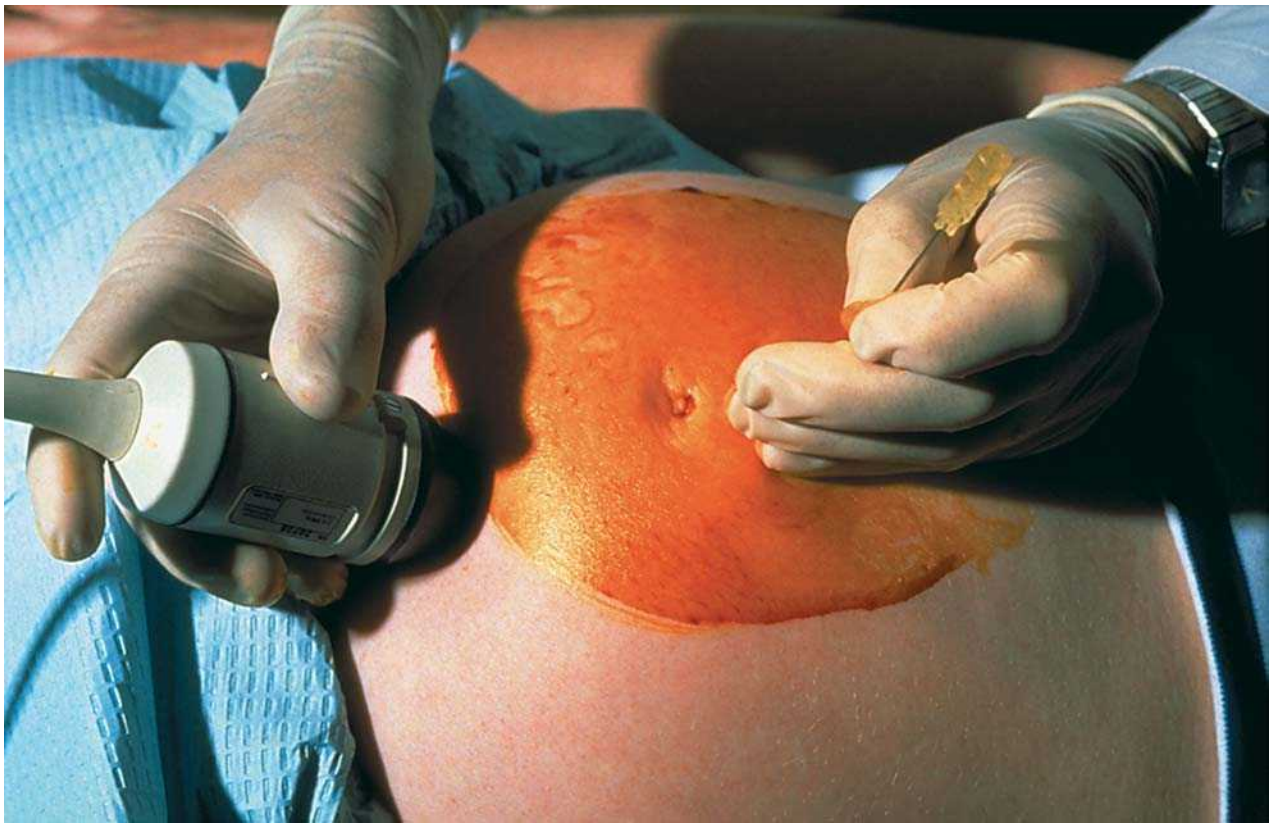
Many laboratories are beginning to incorporate a special technique called *fluorescence in situ hybridization* (FISH) into their chromosome studies. This adjunct testing provides limited information about certain chromosomes within one to two days after amniocentesis. It does not replace a complete chromosome study using amniocyte cultures. In fact, FISH results are often reported as preliminary, pending confirmation by cultured results. They can, however, be very useful, particularly when there is already a high level of suspicion of a fetal chromosome abnormality.

FISH is performed using a small sample of uncultured amniotic fluid cells. Special molecular tags for particular chromosomes are used. These tags attach themselves to the chromosome. Under specific laboratory conditions, they can be made to "light up" or fluoresce. Their signals can then be counted using a special kind of microscope. FISH is most often used to quickly identify a change in the number of chromosomes from pairs 13, 18, 21, and the two sex chromosomes, X and Y. Abnormalities of these chromosomes account for nearly 95% of all chromosomal abnormalities. Other chromosomal abnormalities will be missed since FISH cannot identify structural rearrangements of the chromosomes or abnormalities involving other pairs. A full chromosome evaluation on cultured cells is a necessary follow-up to interphase FISH results.

A sample of amniotic fluid may be used to measure alpha-fetoprotein (AFP). AFP is a protein made by the fetal liver. It passes out of the fetus and enters both the amniotic fluid and the mother's blood. Screening for open neural tube defects, abnormal openings in the fetal head or spinal cord, or ventral wall defects, openings along the belly wall, can be done by measuring AFP during the fifteenth to twentieth weeks of pregnancy. AFP levels normally show a gradual increase during this time. An unusually high level of serum AFP does not necessarily indicate a problem with fetal development, but is cause for some concern. A high AFP level in amniotic fluid will detect up to 98% of all openings on the fetal body that are not covered by skin. Further studies may be suggested if the AFP is high. Most initial AFP results are available within two to three days after amniocentesis.

Finally, amniotic fluid samples obtained by amniocentesis may also be used for more specialized genetic studies, such as biochemical or DNA testing. Both often require cell cultures and additional time to complete. These studies are not done on every sample. Rather, they are offered to those couples who, based on their family history or other information, are at increased risk of having a child with a single **gene**, or Mendelian, disorder. Hundreds of such disorders have been described. Examples include **Tay-Sachs disease**, **cystic fibrosis**, and **sickle cell anemia**. If biochemical or DNA studies are performed, all of the results may not be ready until three to four weeks after testing, although for each patient, the waiting time may be slightly different.

It is important to emphasize that normal results from tests done on amniotic fluid do not necessarily guarantee the birth of a normal infant. Each couple in the general population faces a risk of roughly 3–4% of having a child with any type of congenital birth defect. Many of these



Amniocentesis may be performed to detect several types of genetic disorders. Here, a physician uses an ultrasound monitor (left) to position the needle for insertion into the amnion during the amniocentesis procedure. *(Photo Researchers, Inc.)*

will not be detected with tests done on amniotic fluid samples obtained by amniocentesis. Babies with birth defects are often born into families with no history of genetic disorders.

Chorionic villus sampling

Mid-trimester amniocentesis has been available for nearly thirty years. Chorionic villus sampling (CVS) has been available in the United States since the 1980s. CVS is usually performed between ten to twelve weeks of pregnancy. It involves the removal of a small sample of the developing placenta, or chorionic villi. It has been an attractive alternative to amniocentesis, particularly for those women who desire both testing and results earlier in their pregnancies. Some of the benefits of earlier testing include reassurance sooner in pregnancy and fewer physical complications following first trimester pregnancy termination, for those couples who choose this option after testing. CVS is, however, associated with a higher risk of miscarriage than mid-trimester amniocentesis. At experienced centers, this risk is approximately 1% (or, 1 in 100).

Early amniocentesis

Early amniocentesis is performed before the thirteenth completed week of pregnancy. It has been considered experimental for many years. The results of the largest early amniocentesis trial, published in 1998, have caused physicians worldwide to reconsider the benefit and risks of this procedure.

The Canadian early and mid-trimester amniocentesis trial (CEMAT) is the largest multi-center, randomized clinical trial of early amniocentesis to date. The purpose of the trial was to examine and compare the safety and accuracy of early (EA) versus mid-trimester amniocentesis (MTA). In order to accomplish this, 4,374 pregnant women were identified and enrolled in the study. Ultrasound was performed in the first trimester to confirm the gestational age of all pregnancies. Computer randomization was used to evenly divide the women into either the EA or MTA groups. Ultimately, 1,916 women underwent EA and 1,775 women had MTA. Follow-up was obtained on nearly all pregnancies. Two striking conclusions were reached: EA is associated with an

increased incidence of **clubfoot** and an increased risk of procedure-related pregnancy loss.

Clubfoot, also referred to as *talipes equinovarus*, occurs in approximately one in 1,000 live births (0.1%) in the general population. It may involve either one foot (unilateral) or both feet (bilateral). Males are affected slightly more often than females. There are several proposed mechanisms by which clubfoot could occur: due to the interaction of several genes during development, as a direct consequence of environmental factors, such as an abnormal position in the uterus, or as a physical component of a single gene disorder. Any such disorder would be expected to also cause other abnormalities.

Overall, the CEMAT study found an incidence of clubfoot in the EA group of 1.3% (29 infants). None of the affected infants had other abnormalities. This is nearly ten times higher than the risk in the general population. The frequency of clubfoot in the MTA group was the same as in the general population (0.1%). Prior studies of mid-trimester amniocentesis did not reveal an increased frequency of infants with clubfoot or other birth defects.

Clubfoot was more common when testing was performed during the eleventh, rather than the twelfth, week of pregnancy. This suggests that there may be a specific window sometime in the eleventh to twelfth weeks during which the fetus may be particularly vulnerable to developing clubfoot. It is possible that EA causes a temporary, but still significant, loss of amniotic fluid. This loss may go unrecognized. However, it could, in turn, affect the flow of blood to the foot or cause direct pressure on the developing limb, either of which could lead to clubfoot. It is difficult to know which potential mechanism could be correct since the number of affected infants born after EA is relatively small.

Of note, a separate, much smaller, study also demonstrated an increased incidence of clubfoot (1.7%) among the set of women who underwent EA. The study consisted of patients randomized between EA and CVS and examined the risk of miscarriage after EA. Enrollment in the study was stopped once the association between EA and clubfoot was identified. There were no birth defects identified after CVS.

An additional concern recognized from CEMAT was a higher rate of miscarriage after EA. A procedure-related loss was defined as one that occurred either shortly after the testing or before twenty weeks of pregnancy. Fifty-five women (2.5%) experienced a miscarriage after EA. In contrast, miscarriage occurred in seventeen (0.8%) of the MTA patients. An increased rate of loss appeared to more often follow technically challenging procedures. Difficult procedures included those pregnancies in which bleeding occurred prior to amniocentesis or in which uterine fibroids were present. Tenting of the membranes also made early amniocentesis difficult. Tenting occurs when the amnion and chorion are not yet completely fused, as is true for the majority of first trimester pregnancies. The separation between the membranes makes insertion of the amniocentesis needle more difficult.

In the absence of a difficult EA procedure, a higher rate of loss was also observed among those pregnancies in which the mother experienced obvious leakage of amniotic fluid or vaginal bleeding after testing. The level of physician experience with EA did not influence the rate of loss.

Finally, EA was also linked to an increased number of laboratory culture failures (no growth of cells and no results) compared to MTA. The total waiting time for results was slightly longer in the EA group. This is not entirely a surprise, since a smaller amount of fluid is obtained when EA is performed. Hence, there are fewer cells, and culturing takes longer.

Demographics

According to the National Center for Health Statistics (NCHS), 112,776 amniocentesis procedures were performed in the United States in 1998, the most recent year for which data is available. The annual birth rate that year was approximately 3.9 million infants. Thus, approximately 3% of pregnant women in the United States had this procedure performed. It is likely that this is an underestimate, however. The NCHS obtains information from birth certificates registered in each state and the District of Columbia. Although almost all deliveries are registered in the United States, records are still submitted with incomplete information. It is also not possible to know how many amniocentesis procedures were performed for genetic testing, as compared to other indications, as this information is not requested.

Summary

Amniocentesis is a reliable procedure for prenatal diagnosis in the second trimester of pregnancy. It is primarily offered to pregnant women who are at increased risk, based on their age, family history, or other factor, of having a child with a genetic condition. Amniocentesis provides accurate information about fetal chromosomes or the likelihood of certain physical abnormalities. Additional specialized studies may be performed on an as-needed basis. Despite these benefits, amniocentesis is associated with a slightly increased chance of pregnancy loss. Each woman should discuss the potential risks and

benefits of amniocentesis with a doctor or genetic counselor to make a decision about whether or not she has this testing. Early amniocentesis, or procedures performed before the thirteenth week of pregnancy, has been associated with an increased risk of clubfoot and of procedure-related pregnancy loss.

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Terri A. Knutel, MS, CGC

Amyotrophic lateral sclerosis

Definition

Amyotrophic lateral sclerosis (ALS) is a fatal disease that affects nerve cells in the brain and spinal cord that are responsible for movement. The motor neurons (nerve cells which send an impulse to illicit muscular contraction or movement) in an ALS patient die as a result of rapid degeneration. Voluntary muscles, controlled by motor neurons, lack proper nourishment and will weaken and atrophy (shrink) as a result. Examples of voluntary movement include stepping off of a curb or reaching for the top shelf. These activities rely on the muscles of the arms and legs. Paralysis sets in at the end-stages of ALS and leaves the patient unable to function physically, despite remaining mentally intact. There are no known causes or cures for amyotrophic lateral sclerosis, and the disease can afflict anyone. The usual cause of death is paralysis of the respiratory muscles which control breathing.

KEY TERMS

Aspiration—Inhalation of food or saliva.

Bulbar muscles—Muscles that control chewing, swallowing, and speaking.

Degeneration—Nerves progressively withering.

Fasciculations—Involuntary twitching of patient's muscles.

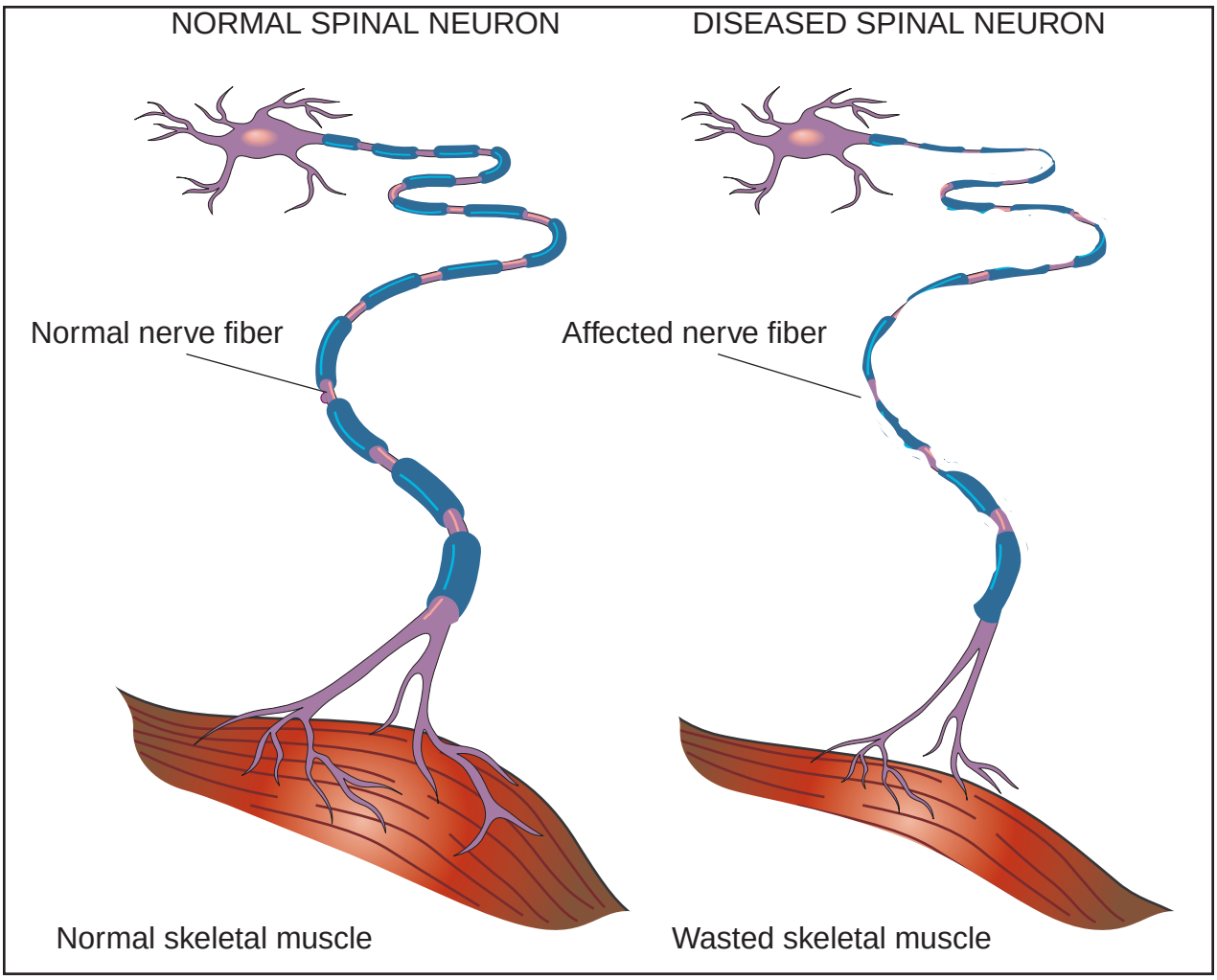
Voluntary muscle—A muscle under conscious control, such as arm and leg muscles.

Description

Amyotrophic lateral sclerosis is a progressive disease of the central nervous system. "A" means "no," "myo" implies muscle cells, and "trophic" refers to nourishment. The nerve cells that extend from the brain to the spinal cord (upper motor neurons), and from the spinal cord to the peripheral nerves (lower motor neurons), for unexplained reasons, degenerate and die. "Lateral" refers to the areas of the spinal cord that are affected, and "sclerosis" occurs as hard tissue replaces the previously originally healthy nerve.

The parts of the body that are not affected by ALS are those areas not involved in the use of motor neurons. The mind remains very sharp and in control of sight, hearing, smell, touch and taste. Bowel and bladder functions are generally not affected. Amyotrophic lateral sclerosis rarely causes pain, yet leaves patients dependent on the care of others during advanced stages.

At any given time there are about 30,000 people in the United States with amyotrophic lateral sclerosis, and about 5,000 new cases are reported each year. ALS pro-



The degeneration and death of motor neurons in the spinal cord and brain results in amyotrophic lateral sclerosis (ALS). These neurons convey electrical messages from the brain to the muscles to stimulate movement in the arms, legs, trunk, neck, and head. As motor neurons degenerate, the muscles are weakened and cannot move as effectively, leading to muscle wasting. *(Gale Group)*

gresses rapidly and paralyzed patients are usually under the intensive care of nursing facilities or loved ones. This can have a devastating psychological effect on the family members and the patient. In most cases, ALS is fatal within two to five years, although approximately 10% live eight years or more.

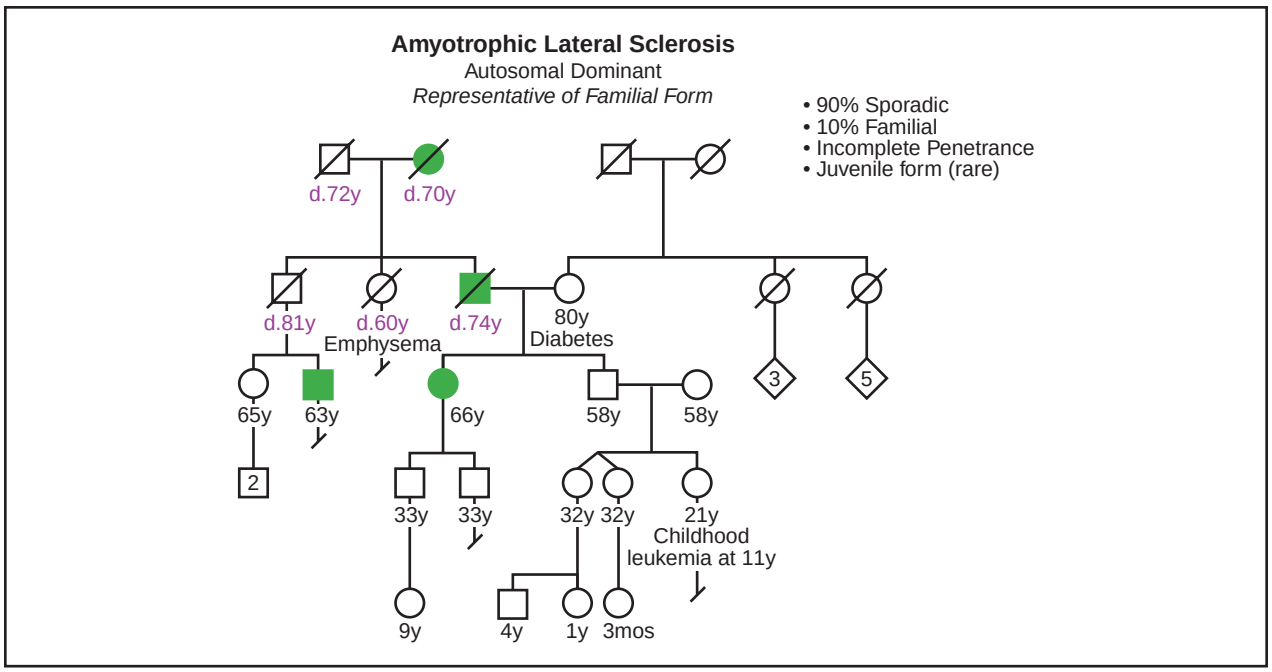
Amyotrophic lateral sclerosis is not a rare disease. ALS affects approximately seven people out of every 100,000. Most people with ALS are between 40 and 70 years of age. Approximately 5–10% of cases show a heredity pattern.

ALS, or Lou Gehrig's disease, is named after the great New York Yankee's first basemen. Lou Gehrig, known as the "Ironman" of baseball, died two years after he was diagnosed with amyotrophic lateral sclerosis.

Genetic profile

In 1991 a team of ALSA researchers linked familial ALS to chromosome 21. In 1993 it was found that there were structural defects in the SOD1 (superoxide dismutase) **gene** on chromosome 21. The SOD1 gene is an enzyme that protects the motor neurons from free radical damage. There is a high incidence of ALS on the island of Guam, in the Western New Guinea and on Kii peninsula of Japan leading some theorists to believe that genetic makeup may be susceptible to an environmental cause, such as the high levels of mercury and lead in these areas.

The **inheritance** pattern is autosomal dominant, which means that children of an affected parent have a 50% chance of inheriting the disorder. The majority of cases are due to a sporadic **gene mutation**, which means



(Gale Group)

the mutation ocurrs only in the affected person. It is thought that sporadic mutations result from both biological and environmental causes. In rare cases, a mutation in NFH, the gene encoding for neurofilament (a structure that maintains cell shape) is apparent. Familial amyotropic lateral sclerosis has been linked to other chromosomal locations but the exact genes involved have not been identified. The Institutional Review Board at Thomas Jefferson University in Philadelphia recently approved the ALS **gene therapy** project. The goal of the project is to inject an adeno-associated virus carrying a normal copy of an EAAT2 gene into an ALS patient's spinal cord where the motor neurons are dying. The hope is that the cells in that area will not die off.

Demographics

Amyotrophic lateral sclerosis affects anyone and both men and women are at equal risk. ALS may occur at any age, and the odds of developing it increase with age. There have been reported cases of teenagers with ALS. A person only needs to inherit a defective gene from one parent to cause the disease.

Signs and symptoms

The disease starts slowly, affecting just one limb, such as the hands or feet, and steadily progresses to more limbs and muscles. When muscles lack the proper nourishment they require, they begin to thin and deteriorate. This condition is the hallmark of amyotrophic lateral sclerosis. Muscle wasting is due to the inability of degenerating motor neurons to elicit a signal to the muscles that allow them to function and grow. Common examples of symptoms for ALS are muscle cramps and twitching, weakness in the hands, feet, or ankles, speech slurring, and swallowing difficulties. Other early symptoms include arm and leg stiffness, foot drop, weight loss, fatigue, and difficulty making facial expressions.

One of the earliest symptoms of ALS is weakness in the bulbar muscles. These muscles in the mouth and throat assist in chewing, swallowing, and speaking. Weakness of these muscle groups usually cause problems such as slurred speech, difficulty with conversation and hoarseness of the voice.

Another symptom of ALS that usually occurs after initial symptoms appear is persistent muscle twitching (fasciculation). Fasciculation is almost never the first sign of ALS.

As the disease progresses the respiratory muscles (breathing muscles) weaken, resulting in increased difficulty with breathing, coughing, and possibly inhaling food or saliva. The potential for lung infection increases and can cause death. Many patients find it more comfortable and extend their lives when assisted by ventilators at this stage of the disease. Communication becomes very difficult. One way to accomplish feedback with others is to make use of the eyes. Blinking is one mode that

patients of amyotrophic lateral sclerosis will be forced to utilize, in order to continue communication.

As the disease progresses, victims gradually lose the use of their feet, hand, leg, and neck muscles, and paralysis results in affected muscle groups. They are able to speak and swallow only with great struggle. Sexual dysfunction is not affected. Breathing will become increasingly difficult and the patients of ALS may decide to prolong life with the use of assisted ventilation, which may decrease the risks of death from infections such as pneumonia.

Diagnosis

ALS is difficult to diagnose. There is no one set way to test for the disease. A series of diagnostic tests will rule out and exclude other possible causes and diseases that resemble ALS. Electro diagnostic tests such as electromyography (EMG) and nerve conduction velocity (NCV) are used to help diagnose ALS. Blood and urine tests, spinal taps, x rays, and muscle and/or nerve biopsy are performed, as well as magnetic resonance imaging (MRI), myelograms of the cervical spine and a complete neurological exam.

A second opinion is frequently recommended if ALS is suspected since it is a fatal neurological disease. After a complete medical exam and family history check has been administered, other tests such as a CT (computed tomography) scan may be done to continue ruling out other causes. Many symptoms mimic ALS such as tumors of the skull base or upper cervical spinal cord, spinal arthritis, thyroid disease, lead poisoning, and severe vitamin deficiency. Other possibilities to rule out are multiple sclerosis, spinal cord neoplasm, polyarteritis, syringomyelia, **myasthenia gravis**, and **muscular dystrophy**. Amyotrophic lateral sclerosis is hardly ever misdiagnosed after this intensive series of diagnostic tests.

Treatment and management

Currently, there is no treatment for ALS. Management aims to control the symptoms that patients experience. Emotional, psychological, and physical support are provided to ease the difficulty associated with this disorder.

Moderate activities are recommended in the early stages of the disease. Physical therapy can help muscles stay active and delay the resulting weakness. ALS patients are encouraged to maintain a healthy diet and exercise regularly for as long as possible. Education of ALS is very important in developing an understanding of the disease, and is vital for family members as well as patients.

Although there are no set treatments for ALS there are still many special considerations that can assist in the quality of lifestyle for the patient. Implementing a physical therapy program, providing a wheelchair or walker, assistance when bathing, and suction machines to help evacuate accumulated secretions all help the ALS patient. Other considerations include providing foods that are soft and easy to swallow, skin maintenance, feeding tubes, ventilation maintenance and emotional support.

Researchers have developed a drug approved by the Food and Drug Administration (FDA) called Rilutek (riluzole). The drug was the first to have a positive effect in that it appears to extend the life of ALS patients by about three months.

Another drug, Myotrophin (somatomedin C), appears to prevent neuron loss and enhance neuron generation in animal studies.

Prognosis

Amyotrophic lateral sclerosis normally progresses rapidly and leads to death from respiratory infection within three to five years. If the person involved is young and the initial symptoms appear in the limbs, the disease tends to develop more slowly. Improved medical care has prolonged the lives of ALS patients and shows promise for more effective treatments in the future.

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Center for Neurologic Study. 9850 Genesee Ave., Suite 320, Lajolla, CA 92037. (858) 455-5463. Fax: (858) 455-1713. cns@cts.org. <http://www.cnsonline.org>.

Forbes Norris ALS Research Center. California Pacific Medical Center, 2324 Sacramento St., San Francisco, CA 94115. (415) 923-3604. Fax: (415) 673-5184.

Laith Farid Gulli, MD
Brian Veillette, BS

Androgen insensitivity syndrome

Definition

Androgen insensitivity syndrome is a genetic condition where affected people have male **chromosomes** and male gonads (testicles). The external genitals, however, have mild to complete feminization.

Description

Normal sexual development

In normal development, the chromosome sex determines the gonadal sex, which in turns determines the phenotypic sex. The chromosome sex is determined at conception; a male has the sex chromosome pair XY and a female has the chromosome pair XX. During the first 40 days of gestation, a male and female embryo appear the same and have undifferentiated gonads, which have the potential of becoming testes or ovaries. The presence of the Y chromosome in the male directs the undifferentiated gonads to become testicles. If no Y chromosome is present, such as in the female chromosome pair, the undifferentiated gonads become ovaries.

In males, the phenotypic sex, including the internal male structures and the external male genitalia, arises as a result of the hormones secreted from the testicles. The two main hormones secreted by the testicles are testosterone and mullerian duct inhibitor. Testosterone acts directly on the wolffian duct, which give rise to the internal male structures including the epididymides, vasa deferentia, and seminal vesicles. Testosterone is converted into dihydrotestosterone, the hormone responsible for the development of the male urethra and prostate, and the external genitalia of the penis and the scrotum. The mullerian duct inhibitor is the hormone that suppresses the mullerian ducts and prevents the development of fallopian tubes, upper vagina, and uterus in males.

If no testicles are present, as with females, no mullerian duct inhibitor is formed and the mullerian ducts become the fallopian tubes, the upper vagina, and the uterus. The wolffian ducts regress. Due to the lack of dihydrotestosterone, the external genitals are not masculinized and become female. Studies have shown that an ovary is not required for the formation of the internal female structures or the feminization of the genitals. If a testicle is not present, the development of the embryo will default to female development.

In most cases, the chromosomal sex, the gonadal sex, and the phenotypic sex are in agreement. Males have 46,XY chromosomes, testicles, and male internal structures and genitals. Females have 46,XX chromosomes, ovaries, and internal female structures and genitals.

Androgen insensitivity syndrome

Androgen insensitivity syndrome (AIS), also known as testicular feminization, is one of the most common conditions where the chromosome sex and gonadal sex do not agree with the phenotypic sex. Affected people have normal male chromosomes, 46,XY and testicles. The testicles secrete both testosterone and mullerian duct inhibitor as normal and no internal female structures form. However, due to defective androgen receptors, the wolffian ducts and genitals cannot respond to the androgens testosterone and dihydrotestosterone. As a result, no male internal structures are formed from the wolffian ducts and the external genitals are feminized.

The amount of feminization depends on the severity of the androgen receptor defect and is often characterized as complete androgen insensitivity (CAIS), partial androgen insensitivity (PAIS), and mild androgen insensitivity (MAIS). In complete androgen insensitivity, the alteration in the androgen receptor results in complete female

KEY TERMS

Androgens—A group of steroid hormones that stimulate the development of male sex organs and male secondary sexual characteristics.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Mullerian ducts—Structures in the embryo that develop into the fallopian tubes, the uterus, the cervix and the upper vagina in females.

Wolffian ducts—Structures in the embryo that develop into epididymides, vasa deferentia, and seminal vesicles in males.

TABLE 1

Classification of AIS Phenotypes

Type	External genitalia (synonyms)	Findings
CAIS	Female ("testicular feminization")	Absent or rudimentary wolffian duct derivatives Inguinal or labial testes; short blind-ending vagina Little or no pubic and/or axillary hair
CAIS or PAIS	Predominantly female (incomplete AIS)	Inguinal or labial testes Labial fusion and enlarged clitoris Distinct urethral and vaginal openings or a urogenital sinus
PAIS	Ambiguous	Microphallus (<1 cm) with clitoris-like underdeveloped glans; labia majora-like bifid scrotum Descended or undescended testes Perineoscrotal hypospadias or urogenital sinus Excessive development of the male breasts during puberty
	Predominantly male	Simple (glandular or penile) or severe (perineal) "isolated" hypospadias with a normal-sized penis and descended testes or severe hypospadias with micropenis, bifid scrotum, and either descended or undescended testes Excessive development of the male breasts during puberty
MAIS	Male (undervirilized male syndrome)	Impaired sperm development and/or impaired masculinization Overdevelopment of the male breasts during puberty

external genitals. In partial androgen insensitivity, also called Reifenstein syndrome, partial androgen insensitivity results in female genitalia with some masculinization, ambiguous genitalia, or male genitalia with partial feminization. With mild androgen insensitivity, mild androgen resistance results in normal male genitals or a male with mild feminization.

In both CAIS and PAIS, affected individuals are sterile (can not have a child). In MAIS, the affected male may have fertility problems because of oligospermia, low sperm production, or azoospermia, no sperm production. In all types of AIS, secondary sex characteristics such as body and pubic hair can be abnormal. Mental impairment is not found in any of the types of androgen insensitivity syndromes, though poor visual-spatial ability has been observed. People with AIS can also be rather tall, though bone age is usually normal.

Genetic profile

Androgen insensitivity syndrome is a genetic condition that results from mutations (alterations) of the **gene** for the androgen receptor. The androgen receptor is located on the long arm of the X chromosome (Xq11-q12). As women have two X-chromosomes, they also have two androgen receptor genes. Men have only one X chromosome and a Y chromosome; hence they only have one copy of the androgen receptor gene.

When women have one copy of the androgen receptor altered, they are considered carriers of AIS. In most cases, the second, normal copy of the androgen receptor can compensate for the altered copy. However, in approximately 10% of women who are carriers for the altered androgen receptor gene, clinical signs such as sparse pubic hair and armpit hair or a delay to the start of their first menstrual period is observed.

46,XY conceptions that have alterations in the androgen receptor gene do not have a second copy to compensate for the altered copy. Hence, these people will have AIS. If the androgen receptor is severely altered, they will have CAIS. If not severely altered, they will have PAIS or MAIS.

All forms of AIS are inherited in an X-linked recessive pattern. This means women who are carriers have a 25% chance of having an affected child. If a carrier woman has a 46,XY conception, there is a 50% chance the child will have AIS. If a carrier woman has a 46,XX conception, there will be a 50% chance the daughter will also be a carrier.

When a person has AIS and has no other family history of the condition, approximately 2/3 of the time the affected person inherited the gene alteration from his or her mother. The other 1/3 of the time, the alteration of the androgen receptor was a new event (new mutation) in the affected person and was not inherited.

Cases of both gonadal mosaicism and somatic mosaicism have been reported with AIS. Gonadal mosaicism occurs when the alteration in the androgen receptor occurred not at conception, but in one of the gamete cells (sperm or egg). The rest of the cells of the body do not have the altered androgen receptor. With AIS, this can occur when one of a woman's early gamete cell has the new alteration in the androgen receptor but the rest of the cells in her body do not. All the eggs that come from the early gamete cell will also have the alteration. Her risk for having a child with AIS is increased. Somatic mosaicism occurs when the alteration in the

androgen receptor occurs after conception but not in a gamete cell. Some of the person's cells will have the altered androgen receptor and other cells will not. The amount of cells with altered receptors and the location of those cells within the body will determine how severely affected a person will be.

Mutations within the androgen receptor gene are also responsible for the neuromuscular condition spinobulbar muscular atrophy or **Kennedy disease**. See separate entry for more information.

Demographics

Complete androgen insensitivity syndrome occurs in approximately 1/64,000 46,XY births or 2-5/100,000 births overall. Partial AIS is at least as common as complete AIS. The incident of mild AIS is unknown, but is estimated to account for approximately 40% of male infertility due to severe oligospermia or azoospermia.

Signs and symptoms

Complete androgen insensitivity

Individuals with CAIS are born looking like normal female babies. Often, the condition is discovered in one of two ways. The child can have an inguinal hernia that upon repair is found to contain testicles. The most common presentation is during puberty with primary amenorrhea, or lack of the onset of the menstrual period. Affected individuals have a short, blind ending vagina and no uterus, cervix, fallopian tubes, or ovaries. During puberty, some girls will have absent or decreased sexual hair. Breasts develop normally and can be large in size with pale and immature nipples and areola. People with CAIS are usually raised as females and have normal female sexual orientation. All women with CAIS are sterile. In families with CAIS, all affected members will have complete androgen insensitivity and similar physical features.

Partial androgen insensitivity syndrome

Children with PAIS usually present at birth due to ambiguous genitalia. The genitalia can look like female genitals with some masculinization, completely ambiguous genitals where the sex of the baby cannot be immediately determined, or male genitals with some feminization. The degree of severity is a direct result of the degree of severity of the genetic alteration in the androgen receptor and resulting amount of functional androgen receptor. The internal structures of PAIS are the same as CAIS, with absent fallopian tubes, cervix, uterus, and ovaries. Testes are present but do not produce sperm. Hence, people with PAIS are also sterile. People with PAIS also have primary amenorrhea, and breast development occurs in puberty. Unlike CAIS, affected individuals in the same family with presumably the same genetic alteration can have varying degrees of masculinization. As a result, some affected people may be raised as females whereas others may be raised as males. Sex assignment is made based upon the structure of the genitals, the surgical correction needed, and the predicted response to androgens during puberty.

Mild androgen insensitivity

Males with mild androgen insensitivity usually have normal male genitals and internal male structures. During puberty, males with MAIS may have breast enlargement, sparse facial and body hair, and small penis. Some affected males may also have impaired sperm production resulting in oligospermia or azoospermia, decreased or absent sperm. As with CAIS, affected men within the same family usually have similar features.

Diagnosis

Diagnosis is usually made based upon clinical features, chromosome analysis, hormone levels, and analysis of androgen receptor function in skin fibroblasts. Clinical features are listed above for CAIS, PAIS, and MAIS. Chromosome analysis reveals normal male chromosomes. Affected individuals can have elevated luteinizing hormone, normal to slightly elevated testosterone, and high estradiol for men. Follicle stimulating hormone may also be normal to elevated. Reduced androgen receptor function in skin fibroblast cells is also used to aid in a diagnosis.

As of 2001, direct **genetic testing** for molecular defects in the androgen receptor gene is being done on a research basis only.

Treatment and management

Complete androgen insensitivity

Treatment of CAIS requires the removal of the testicles from the pelvis or inguinal canal to decrease risk of testicular malignancy. Because the overall risk of malignancy is approximately 5% and rarely occurs before age 25, the testicles are usually removed after the development of the secondary sex characteristics, as the testes are needed for estrogen formation. After the removal of the testes, estrogen supplementation is started to aid in

the development of secondary sex characteristics and to help prevent osteoporosis. Surgery to lengthen the vagina may be necessary.

Partial androgen insensitivity syndrome

For those affected individuals raised as females, treatment is similar to CAIS except the removal of the testicles is done earlier because it may cause enlargement of the clitoris during puberty. Reconstructive surgery of the genitals and lengthening of the vagina may be necessary.

People with PAIS raised as boys may need surgery to improve the appearance of the genitals. Androgen supplementation may be implemented, though long-term affects of androgen therapy are not known. Breast reduction surgery may be necessary after puberty.

Mild androgen insensitivity

Males with MAIS may require no treatment at all or breast reduction surgery after puberty. Males who are infertile may benefit from assisted reproductive technologies.

Prognosis

For CAIS and MAIS, the prognosis is excellent. Generally, gender assignment is not difficult and sexual orientation is female for CAIS and male for MAIS. Treatment usually involves minimal surgery and hormone supplementation. For individuals with PAIS, the prognosis is very dependent upon the severity of the condition. Assignment of gender can be difficult and genital surgery can be more involved. Recently, some individuals with PAIS and other intersex conditions have encouraged the delay of assigning gender until the child is old enough to express a preference. As of 2001, this idea has not been readily embraced in the medical community of the United States.

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Intersex Society of North America. PO Box 301, Petaluma, CA 94953-0301. <http://www.isna.org>.

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Carin Lea Beltz, MS, CGC

Anemia, sideroblastic X-linked

Definition

X-linked sideroblastic anemia is a hereditary enzyme disorder in which the body has adequate iron but is unable to incorporate it into hemoglobin.

Description

X-linked sideroblastic anemia is the hereditary form of sideroblastic anemia, also known as iron overload anemia or sideroblastosis. Another, more common type of sideroblastic anemia is called acquired sideroblastic anemia.

In sideroblastic anemia, iron enters a developing red blood cell and is not incorporated properly into the hemoglobin molecule (the cell's oxygen carrier). This causes iron to accumulate in the mitochondria and sideroblasts. The defective hemoglobin then transports oxygen poorly, resulting in decreased tissue oxygenation.

This build–up of iron gives the cell nucleus its ringed appearance, called ringed sideroblast, which is the primary sign of siderblastic anemia.

Sideroblastic anemia is often mistaken for iron deficiency anemia, but tests usually reveal normal or increased levels of iron.

X-linked sideroblastic anemia

The hereditary form of the disorder is rare. The primary type of inherited sideroblastic anemia was first described in 1945 by Thomas Cooley. He identified cases of X-linked sideroblastic anemia in two brothers from a family with a six-generational history of the inherited disease. The genetic abnormality that causes X-linked sideroblastic anemia was identified almost 40 years later. Identification has aided diagnosis of this disorder.

X-linked sideroblastic anemia nearly always manifests in infancy or childhood.

Other inherited forms of sideroblastic anemia

There are other inherited forms of sideroblastic anemia, which are also rare. A rare autosomal recessive form of inherited sideroblastic anemia occurs in both males and females of affected families. Autosomal dominant **inheritance** has also been reported. The abnormalities that cause these anemias are not yet identified. Also, Pearson's syndrome, an inherited disorder caused by abnormal mitochondria, is sometimes called sideroblastic anemia with marrow cell vacuolization and exocrine pancreatic dysfunction.

Acquired sideroblastic anemia

Acquired sideroblastic anemia often results from prolonged exposure to toxins (such as alcohol, lead, or drugs), or nutritional imbalances (such as deficiency in folic acid or copper or excess in zinc). Other causes may be inflammatory disease, cancerous conditions, or kidney, endocrine, or metabolic disorders. Acquired sideroblastic anemia sometimes surfaces in the context of a myelodysplastic syndrome.

Removal of the toxin or treatment of the underlying disease will reverse this type of sideroblastic anemia.

Acquired anemia is usually seen in patients over 65, particularly in those cases associated with myelodysplasia. The disorder can appear as early as the mid-fifties.

Genetic profile

Hereditary sideroblastic anemia is most commonly inherited as an X-linked recessive trait.

Typical X-linked genetics

The following concepts are important to understanding the inheritance of an X-linked disorder. All humans have two **chromosomes** that determine their gender: females have XX, males have XY. X-linked recessive, also called sex-linked, inheritance affects the genes located on the X chromosome. It occurs when an unaffected mother carries a disease-causing **gene** on at least one of her X chromosomes. Because females have two X chromosomes, they are usually unaffected carriers. The X chromosome that does not have the disease-causing gene compensates for the X chromosome that does. For a woman to show symptoms of the disorder, both X chromosomes would need to have the disease-causing gene. That is why women are less likely to show such symptoms than males.

KEY TERMS

Heme—The iron-containing molecule in hemoglobin that serves as the site for oxygen binding.

Hemochromatosis—Accumulation of large amounts of iron in the tissues of the body.

Hemoglobin—Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Mitochondria—Organelles within the cell responsible for energy production.

Myelodysplasia—A bone marrow disorder that can develop into aplastic anemia requiring bone marrow or stem cell transplantation.

Nucleus—The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

Red blood cells—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

If a mother has a female child, the child has a 50% chance of inheriting the disease gene and being a carrier who can pass the disease gene on to her sons. On the other hand, if a mother has a male child who inherits the disease-causing gene, he will be affected and has a 100% chance of passing the disease gene on to his children. Since the gene is defective and in the XY state there is no normal gene, the singular flawed gene is expressed.

Genetics of X-linked sideroblastic anemia

The genetic abnormality that causes X-linked sideroblastic anemia is a mutation in the erythroid (red blood cell) specific form of delta-aminolevulinate synthase (ALAS2). ALAS2 is the first enzyme in the heme biosynthetic pathway and the mutation, when present, results in the inability to transport the heme (iron) into the hemoglobin, making it ineffective.

The ability to test for this genetic disorder has improved diagnosis.

Demographics

X-linked sideroblastic anemia occurs in young men. It may be seen in maternal uncles and male cousins of men with the disorder.

Autosomal transmitted forms of the disease may occur in both men and women.

Hereditary sideroblastic anemia generally occurs during the first three decades of life especially during adolescence, but it has been diagnosed in patients over 70 years old.

Signs and symptoms

General weakness, fatigue, dizziness, and difficulty breathing are associated with the disorder. Exertion may cause chest pains similar to angina.

The mucous membranes and skin of hands and arms may be pale, possibly with a lemon-yellow cast. Subcutaneous bleeding may occur, causing a brownish-red effect.

Excess iron accumulation, known as **hemochromatosis**, accumulates over years in the bone marrow, liver, heart, and other tissues. This progressive deposition of toxic iron may result in an enlarged spleen or liver, liver disease, diabetes, impotence, arthritic signs, and heart disease, particularly cardiac arrhythmia.

Diagnosis

Using Prussian blue staining, sideroblasts are visible under microscopic examination of bone marrow.

A blood test can indicate sideroblastic anemia. Indicative laboratory results of an iron panel test include:

- High levels for serum iron, serum ferritin, and transferrin iron saturation percentage.
- Low levels for total iron binding capacity and transferrin.
- Normal to high levels for serum transferrin receptor.

Additionally, other signs of sideroblastic anemia include:

- Hemoglobin is generally less than 10.0g/dL.
- Hypochromic (reduced color) cells coexist with normal cells.
- Stainable marrow and hemosiderin is increased.
- Ringed sideroblasts are visible with Prussian blue staining and observable under microscopic examination of bone marrow.
- Red cell distribution width is increased.
- White blood cells and platelets are normal.

Treatment and management

The main objective in treatment of X-linked sideroblastic anemia is to prevent the development of diabetes, cirrhosis, and heart failure from iron overload (hemochromatosis).

X-linked sideroblastic anemia often improves with pyridoxine (vitamin B_6) therapy. Dosage is 50–200 mg, however, pregnant or nursing mothers may wish to limit intake to 100 mg daily.

In cases of extreme anemia, whole red blood cell transfusion may be required. Repeated whole red blood cell transfusion, however, will contribute significantly to existing iron burden in sideroblastic anemia patients. It will likely require chelation therapy with desferrioxamine (Desferal), a drug with iron chelating properties. Desferrioxamine binds excess body iron and promotes excretion by the liver and kidneys. It is administered by intravenous infusion from a small portable pump. The pump is worn nine to twelve hours daily, usually at night while sleeping. Side effects vary and include pain and swelling at injection site.

Certain drugs are sometimes associated with acquired sideroblastic anemia: progesterone (found in oral contraceptives and hormone replacement therapy); copper chelating drugs like trientine, which is used in treating **Wilson disease**; and anti-tuberculosis drugs like isoniazid (a type of antibiotic), among others. In other cases, acquired sideroblastic anemia may be secondary to another disorder or disease. Other predisposing causes may be inflammatory disease such as rheumatoid arthritis, cancerous conditions such as leukemia and lymphoma, kidney disorders causing uremia, endocrine disorders such as hyperthyroidism, and metabolic disorders such as porphyria cutanea tarda. In these cases, it is important to treat the primary disease or disorder in order to reverse the anemia.

Development of leukemia is associated with the acquired form of the disease, often first showing up in the form of a myeloproliferative disorder. These disorders are characterized by abnormal growth of bone tissue and related cells

Prognosis

The disorder can often be kept in check with regular medical supervision. Many individuals with X-linked sideroblastic anemia require chronic transfusion to maintain acceptable hemoglobin levels. Over a lifetime, problems related to iron overload, including congestive heart failure and cirrhosis, can become life-threatening issues.

Death can result from hemochromatosis (iron-overload) if the disease is untreated or if blood transfusions are inadequate to account for the iron overload.

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Leukemia & Lymphoma Society. 1311 Mamaroneck Ave., White Plains, NY 10605. (914) 949-5213. <http://www.leukemia-lymphoma.org>.

National Heart, Lung, and Blood Institute. PO Box 30105, Bethesda, MD 20824-0105. (301) 592-8573. nhlbiinfo@rover.nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

Iron Disorders Institute. <http://www.irondisorders.org>.

National Center for Biotechnology Information. <http://www.ncbi.nlm.nih.gov>.

Jennifer F. Wilson, MS

Anencephaly

Definition

Anencephaly is a lethal birth defect characterized by the absence of all or part of the skull and scalp and malformation of the brain.

Description

Anencephaly is one of a group of malformations of the central nervous system collectively called neural tube defects. Anencephaly is readily apparent at birth because of the absence of the skull and scalp and with exposure of the underlying brain. The condition is also called acrania (absence of the skull) and acephaly (absence of the head). In its most severe form, the entire skull and scalp are missing. In some cases, termed "meroacrania" or "meroanencephaly," a portion of the skull may be present. In most instances, anencephaly occurs as an isolated birth defect with the other organs and tissues of the body forming correctly. In approximately 10% of cases, other malformations coexist with anencephaly.

KEY TERMS

Alpha-fetoprotein (AFP)—A chemical substance produced by the fetus and found in the fetal circulation. AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

Genetic profile

As an isolated defect, anencephaly appears to be caused by a combination of genetic factors and environmental influences that predispose to faulty formation of the nervous system. The specific genes and environmental insults that contribute to this multifactorial causation are not completely understood. It is known that nutritional insufficiency, specifically folic acid insufficiency, is one predisposing environmental factor and that mutations of genes involved in folic acid metabolism are genetic risk factors. The recurrence risk after the birth of an infant with anencephaly is 3-5%. The recurrence may be anencephaly or another neural tube defect, such as **spina bifida**.

Demographics

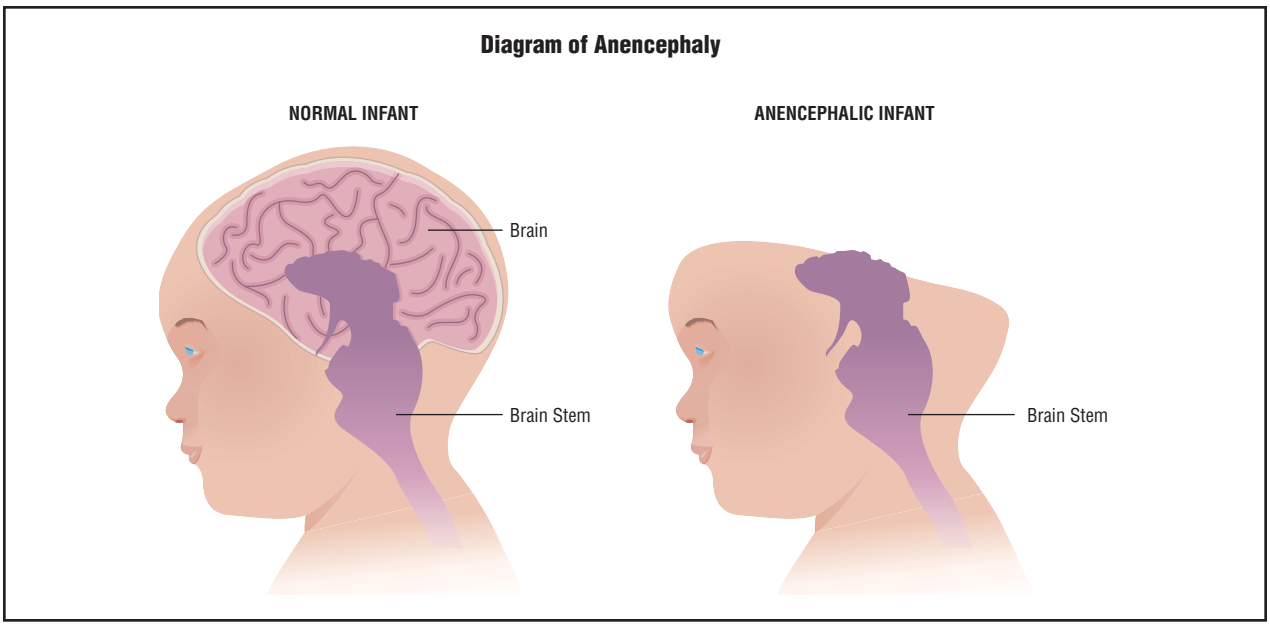
Anencephaly occurs in all races and ethnic groups. The prevalence rates range from less than one in 10,000 births (European countries) to more than 10 per 10,000 births (Mexico, China).

Signs and symptoms

Anencephaly is readily apparent at birth because of exposure of all or part of the brain. Not only is the brain malformed, but it is also damaged because of the absence of the overlying protective encasement. In about 10% of cases of anencephaly, other malformations are also present.

Diagnosis

Anencephaly is diagnosed by observation. Prenatal diagnosis may be made by ultrasound examination after 12 to 14 weeks' gestation. Prenatal diagnosis of anencephaly can also be detected through maternal serum alpha-fetoprotein screening. The level of alpha-fetoprotein in the maternal blood is elevated because of the leakage of this fetal protein into the amniotic fluid.



Infants born with anencephaly have either a severly underdeveloped brain or total brain absence. A portion of the brain stem usually protrudes through the skull, which also fails to develop properly. *(Gale Group)*

Treatment and management

No treatment is indicated for anencephaly. Affected infants are stillborn or die within the first few days of life. The risk for occurrence or recurrence of anencephaly may be reduced by half or more by the intake of folic acid during the months immediately before and after conception. Natural folic acid, a B vitamin, may be found in many foods (green leafy vegetables, legumes, orange juice, liver). Synthetic folic acid may be obtained in vitamin preparations and in certain fortified breakfast cereals. In the United States, all enriched cereal grain flours have been fortified with folic acid.

Prognosis

Anencephaly is uniformly fatal at birth or soon thereafter.

Resources

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March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Birth Defects Prevention Network. Atlanta, GA (770) 488-3550. <http://www.nbdpn.org>.

Roger E. Stevenson, MD

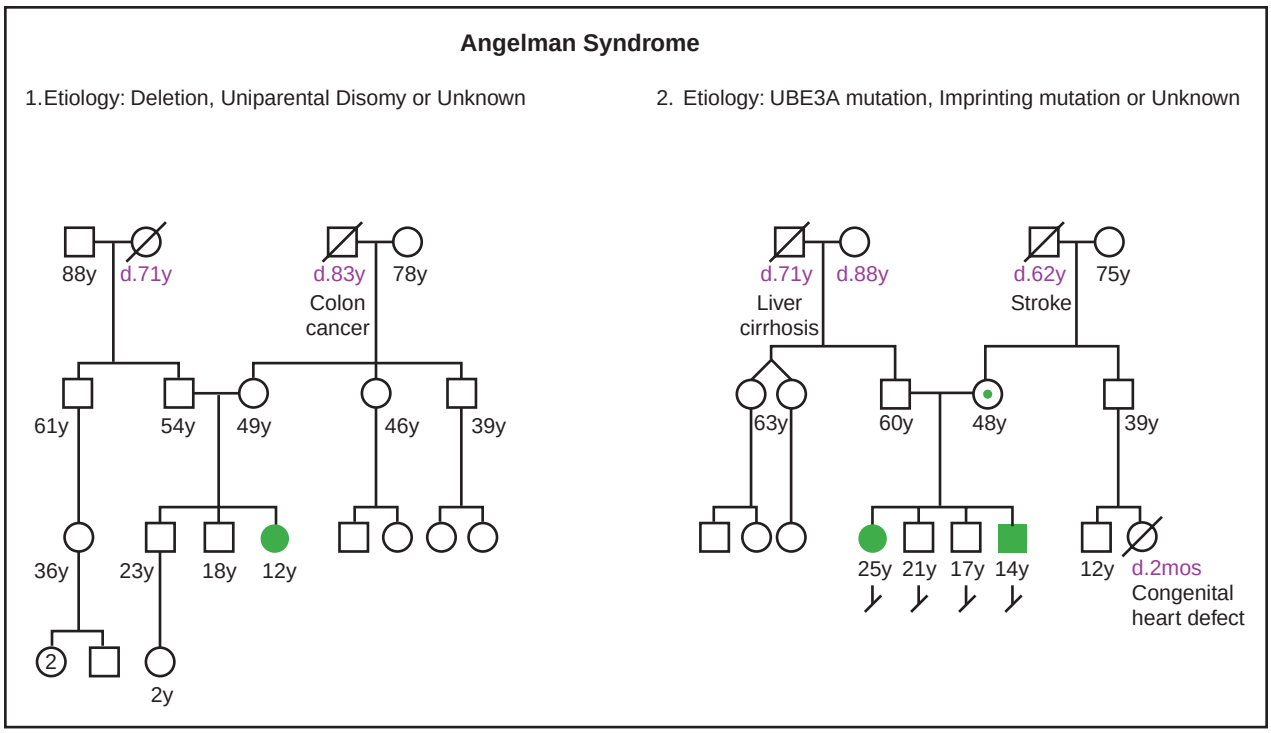
Angelman syndrome

Definition

Angelman syndrome (AS) is a genetic condition that causes severe mental retardation, severe speech impairment, and a characteristic happy and excitable demeanor.

Description

Individuals with AS show evidence of delayed development by 6–12 months of age. Eventually, this delay is recognized as severe mental retardation. Unlike some genetic conditions causing severe mental retarda-



(Gale Group)

tion, AS is not associated with developmental regression (loss of previously attained developmental milestones).

Severe speech impairment is a striking feature of AS. Speech is almost always limited to a few words or no words at all. However, receptive language skills (listening to and understanding the speech of others) and nonverbal communication are not as severely affected.

Individuals with AS have a balance disorder, causing unstable and jerky movements. This typically includes gait ataxia (a slow, unbalanced way of walking) and tremulous movements of the limbs.

AS is also associated with a unique "happy" behavior, which may be the best-known feature of the condition. This may include frequent laughter or smiling, often with no apparent stimulus. Children with AS often appear happy, excited, and active. They may also sometimes flap their hands repeatedly. Generally, they have a short attention span. These characteristic behaviors led to the original name of this condition, the "Happy Puppet" syndrome. However, this name is no longer used as it is considered insensitive to AS individuals and their families.

Genetic profile

The genetics of AS are complex. There are at least five different genetic abnormalities that can cause the condition, all of which involve a specific region of the chromosome 15 inherited from the mother. This region is designated 15q11-13 (bands 11 through 13 on the long arm of chromosome 15). The fact that AS occurs only when there are abnormalities in this region of the maternal copy of chromosome 15 reflects a unique phenomenon known as imprinting. Imprinting is a chemical modification of **DNA** which acts as an "identification tag" indicating which parent contributed the chromosome. Imprinted genes or chromosome regions are expressed or not expressed depending on which parent transmitted the chromosome. Abnormalities in the paternally inherited 15q11-13 region (from the father) cause a different genetic condition called **Prader-Willi syndrome**.

Chromosome deletion

The most common cause of AS is a small deletion (missing piece) in the maternally inherited chromosome 15. Specifically, the deletion occurs within 15q11-13. Approximately 70% of AS individuals have this deletion.

UBE3A mutation

In approximately 11% of AS cases, there is a mutation within the maternally inherited UBE3A **gene**. All the genetic mechanisms leading to AS appear to compromise expression of this gene, which is located within the 15q11-13 region. This gene is considered to be the "critical gene" responsible for AS, although its specific function is unknown.

Uniparental disomy

Some cases of AS result from **inheritance** of both **chromosomes** in the 15 pair from the father, an unusual genetic phenomenon known as uniparental disomy. In this circumstance, there is no chromosome 15 from the mother. Approximately 7% of AS cases result from this mechanism.

Imprinting defect

Approximately 3% of AS cases result from an imprinting defect on the maternally inherited chromosome 15. As noted above, imprinting is a chemical modification to the DNA which serves as a marker indicating the parent of origin and controls gene expression. If there is defective imprinting on the maternally inherited 15, then the genes in the 15q11-15q13 region may not be expressed, leading to AS.

Chromosome rearrangement

Rarely, AS may be caused by chromosomal breaks that occur in the maternal inherited 15q11-13 region. The breaks may occur as the result of a translocation (in which two chromosomes break and exchange material) or an inversion (in which a piece of a chromosome breaks and rejoins in the opposite orientation), or other disturbance of the chromosome structure involving the maternal 15q11-15q13. This mechanism is responsible for about 1% of AS cases.

Unknown mechanism(s)

In about 8% of individuals with AS, no genetic cause can be identified. This may reflect misdiagnosis, or the presence of additional, unrecognized mechanisms leading to AS.

Demographics

AS has been reported in individuals of diverse ethnic backgrounds. The incidence of the condition is estimated at 1/10,000 to 1/30,000.

Signs and symptoms

The first abnormalities noted in an infant with AS are often delays in motor milestones (those related to physical skills, such as sitting up or walking), muscular hypotonia (poor muscle tone), and speech impairment. Some infants seem unaccountably happy and may exhibit fits of laughter. By age 12 months, 50% of infants with AS have microcephaly (a small head size). Tremulous movements are often noted during the first year of life.

Seizures occur in 80% of children with AS, usually by three years of age. No major brain lesions are typically seen on cranial imaging studies.

The achievement of walking is delayed, usually occurring between two-and-a-half and six years of age. The child with AS typically exhibits a jerky, stiff gait, often with uplifted and bent arms. About 10% of individuals with AS do not walk. Additionally, children may have drooling, protrusion of the tongue, hyperactivity, and a short attention span.

Many children have a decreased need for sleep and abnormal sleep/wake cycles. This problem may emerge in infancy and persist throughout childhood. Upon awakening at night, children may become very active and destructive to bedroom surroundings.

The language impairment associated with AS is severe. Most children with AS fail to learn appropriate and consistent use of more than a few words. Receptive language skills are less severely affected. Older children and adults are able to communicate by using gestures or communication boards (special devices bearing visual symbols corresponding to commonly used expressions or words).

Some individuals with AS caused by a deletion of the 15q11-q13 chromosomal region may have a lighter skin complexion than would be expected given their family background.

Diagnosis

The clinical diagnosis of AS is made on the basis of physical examination and medical and developmental history. Confirmation requires specialized laboratory testing.

There is no single laboratory test that can identify all cases of AS. Several different tests may be performed to look for the various genetic causes of AS. When positive, these tests are considered diagnostic for AS.

DNA methylation studies

DNA methylation studies determine if the normal imprinting pattern associated with the maternal

(mother's) copy of the number 15 chromosome is present. The 15q11-q13 region is differently methylated (or "imprinted") depending on which parent contributed the chromosome. If an individual has a deletion of this region on the maternal chromosome 15, paternal uniparental disomy of the number 15 chromosomes (with no number 15 chromosome from the mother), or a defective imprinting mechanism, DNA methylation studies will be abnormal and indicate AS. This test detects the majority (approximately 78%) of cases of AS. Additional studies are then required to determine which of these three mechanisms lead to AS development.

UBE3A mutation analysis

Direct DNA testing of the UBE3A gene is necessary to detect cases of AS caused by mutations in this gene. Cases of AS caused by UBE3A mutations usually have a normal imprinting pattern.

Fluorescent in situ hybridization (FISH)

FISH studies may be necessary to detect chromosome rearrangements that disrupt the 15q11-q13 region on the maternal copy of chromosome 15. The FISH method is a special way of checking for the presence, absence, or rearrangement of very small pieces of chromosomes. FISH testing can also readily detect AS caused by chromosome deletions, which account for approximately 70% of AS cases. FISH testing is often performed following an abnormal methylation study to determine if a chromosome deletion accounts for the abnormal methylation pattern.

Treatment and management

There is no specific treatment for AS. A variety of symptomatic management strategies may be offered for hyperactivity, seizures, mental retardation, speech impairment, and other medical problems.

The typical hyperactivity in AS may not respond to traditional behavior modification strategies. Children with AS may have a decreased need for sleep and a tendency to awaken during the night. Drug therapy may be prescribed to counteract hyperactivity or aid sleep. Most families make special accommodations for their child by providing a safe yet confining environment.

Seizures in AS are usually controllable with one or more anti-seizure medications. In some individuals with severe seizures, dietary manipulations may be tried in combination with medication.

Children with AS appear to benefit from targeted educational training. Physical and occupational therapy may improve the disordered, unbalanced movements typical of AS. Children with a severe balance disorder may require special supportive chairs. Speech therapy is often directed towards the development of nonverbal communication strategies, such as picture cards, communication boards, or basic signing gestures.

Individuals with AS may be more likely to develop particular medical problems which are treated accordingly. Newborn babies may have difficulty feeding and special bottle nipples or other interventions may be necessary. Gastroesophageal reflux (heartburn) may lead to vomiting or poor weight gain and may be treated with drugs or surgery. Constipation is a frequent problem and is treated with laxative medications. Many individuals with AS have strabismus (crossed eyes), which may require surgical correction. Orthopedic problems, such as tightening of tendons or **scoliosis**, are common. These problems may be treated with physical therapy, bracing, or surgery.

Prognosis

Individuals with AS have significant mental retardation and speech impairment that are considered to occur in all cases. However, they do have capacity to learn and should receive appropriate educational training.

Young people with AS typically have good physical health aside from seizures. Although life span data are not available, the life span of people with AS is expected to be normal.

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ORGANIZATION

Angelman Syndrome Foundation, Inc. 414 Plaza Drive, Suite 209, Westmont, IL 60559. (800) IF-ANGEL or (630) 734-9267. Fax: (630) 655-0391. Info@angelman.org. <http://www.angelman.org>.

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Jennifer Ann Roggenbuck, MS, CGC

KEY TERMS

Ankylosis—Immobility of a joint due to the formation of new bone at the site of inflammation.

Cervicitis—Inflammation of the cervix.

Enthesitis—Inflammation at the place where the ligaments insert into the bone.

Enthesopathy—Disorder of the ligament attachment to the bone.

HLA-B27—Stands for a specific form of human leukocyte antigen, the proteins involved in immune system function. Strongly associated with ankylosing spondylitis.

Human leukocyte antigens (HLA)—Proteins that help the immune system function, in part by helping it to distinguish 'self' from 'non-self'.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Osteoporosis—Loss of bone density that can increase the risk of fractures.

Psoriasis—A common, chronic, scaly skin disease.

Rheumatoid arthritis—Chronic, autoimmune disease marked by inflammation of the membranes surrounding joints.

Rheumatoid factor—Antibodies present in the majority of individuals with rheumatoid arthritis. A diagnostic marker for rheumatoid arthritis that is absent from ankylosing spondylitis and other seronegative spondyloarthopathies.

Sacroiliac joint—The joint between the triangular bone below the spine (sacrum) and the hip bone (ilium).

Sacroiliitis—Inflammation of the sacroiliac joint.

Sensitivity—The proportion of people with a disease who are correctly diagnosed (test positive based on diagnostic criteria). The higher the sensitivity of a test or diagnostic criteria, the lower the rate of 'false negatives,' people who have a disease but are not identified through the test.

Specificity—The proportion of people without a disease who are correctly classified as healthy or not having the disease (test negative based on diagnostic criteria). The higher the specificity of a test or diagnostic criteria, the lower the number of 'false positives,' people who don't have a disease but who 'test' positive.

Spondyloarthritis (spondylitis)—Inflammatory disease of the joints of the spine.

Urethritis—Inflammation of the urethra.

Uveitis—Inflammation of all or part of the uvea, which consists of the middle vascular portion of the eye including the iris, ciliary body, and choroid.

Ankylosing spondylitis

Definition

Ankylosing spondylitis (AS) is a relatively common disease that causes inflammation of the area where ligaments and tendons insert into the bone. The inflammatory process eventually leads to reduced mobility or immobility of affected joints. Specific joints are characteristically involved, notably in the spine and pelvis.

Description

Ankylosing spondylitis belongs to a group of disorders called the seronegative spondyloarthropathies. Each disease in this group is characterized by arthritis affecting the spine, as well as the absence of rheumatoid factor, a diagnostic marker that is present in rheumatoid arthritis and helps distinguish it from the group of diseases that includes AS. AS affects primarily the spine and the sacroiliac joint where the spine meets the hips. Progressive symptoms eventually result in fusion of these joints, pain, and markedly decreased joint mobility. AS is considered an autoimmune disease, meaning that symptoms are the result of the action of the immune system of the body against its own tissues. Although the exact mode of action is unknown, there is a strong association of AS with a specific type of human leukocyte antigen, HLA-B27. HLA are genetically-determined proteins that play an important role in the functioning of the immune response of the body, in that they enable the immune system to distinguish between its own cells and foreign cells. Therefore, HLA type is important in immunity, as well as organ and tissue transplantation.

Genetic profile

AS is considered a multifactorial disorder, or one that is the result of both genetic and environmental fac-

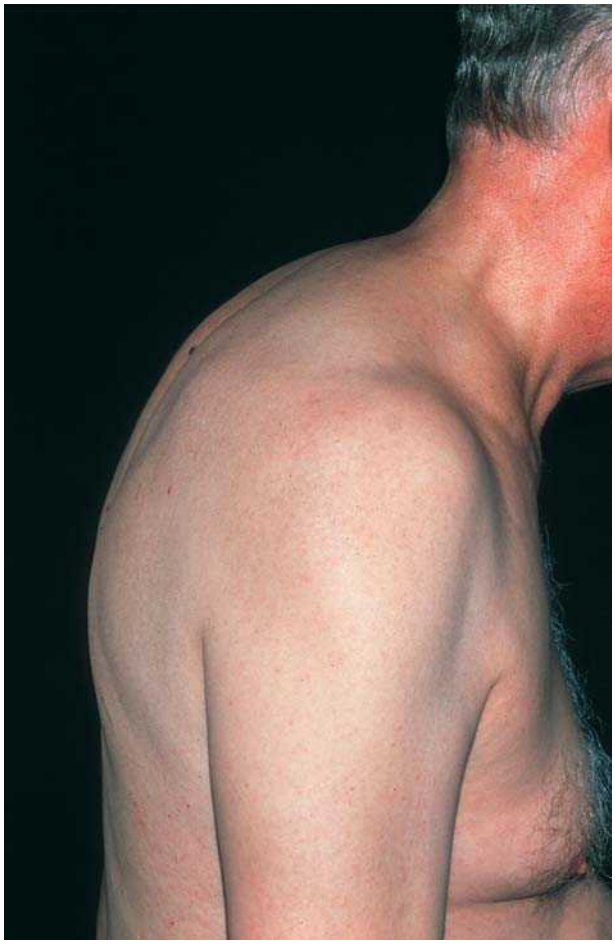
tors interacting. Two genes have been identified that confer susceptibility to AS, both of which are forms of an HLA **gene** on chromosome 6. Some HLA types have been implicated in various autoimmune diseases, meaning diseases in which the immune system attacks the body's own cells and tissues.

The association of HLA B-27 and AS has been clearly established. Ninety-five percent of individuals with AS are B-27 positive, and since AS appears to be a dominant trait, the presence of at least one B-27 allele (a form of the gene) confers a greatly increased chance of developing symptoms. While this population risk may seem relatively high, it is important to realize that only about 9% of the population carries the B-27 allele. Of these individuals who are B-27 positive, only 2–8% will develop AS.

Other environmental and genetic factors most certainly contribute to development of the disease. This becomes more evident when considering that B-27 positive individuals with an affected first-degree relative have a significantly higher chance of developing AS than a B-27 positive individual with no family history. In families with multiple affected members, studies estimate that no more than half of AS recurrence is explained by HLA type. Additionally, there are several B-27 subtypes that have been studied; some confer susceptibility and some do not. Importantly, about 5% of people with AS are B-27 negative. Other environmental and/or genetic factors must certainly be associated with disease in these individuals. Another HLA type—B-60—has also been shown to confer susceptibility, although the association appears to be much weaker and is not seen in all studies. Certain infections are suspected as being necessary for triggering AS in some individuals. In the future, additional susceptibility genes and environmental factors can be expected to be identified.

Demographics

Approximately 0.25% to 1.5% of the population is affected with AS. Prevalence of the disease is comparable to the frequency of the HLA B-27 allele in the population, which varies among ethnic groups. Native North Americans, Alaskan Eskimos, and Norwegian Lapps all have relatively high levels of B-27 and AS. Low levels of B-27 and AS occur among individuals of most types of African ancestry, Australian aborigenes, and Native South Americans. Generally, for every affected female, there are 2-3 affected males.



This 68-year old man has developed an outward curvature of his spine as a result of ankylosing spondylitis. Decreased mobility results as pain and stiffness of the joints between spinal vertebrae progresses. *(Photo Researchers, Inc.)*

Signs and symptoms

The signs of AS vary, but a typical case involves progressive lower back pain and morning stiffness. The immune response at the point where the ligaments or tendons insert into the bones initially causes bone inflammation and fragility, followed by fibrosis, meaning the formation of fiber tissue. The area reacts by forming new bone, which eventually fuses, limiting motion. AS can also affect peripheral joints in a manner similar to other types of arthritis. The vertebral joints of everyone with AS are affected, and 50% of people will also have significant hip arthritis. Osteoporosis in advanced AS commonly results in fractures of the spine.

AS also affects areas other than the bones and joints. An eye complication called *anterior uveitis*, which is easily treated and generally does not affect vision, develops in 5-35% of people with AS. Rarely, the disease may

affect the heart or aorta. Kidney failure is a rare complication. Lung function can be affected due to bone changes that affect the mechanics of breathing. Therefore, individuals with AS should refrain from smoking to avoid early respiratory failure. Ninety percent of affected individuals experience the first symptoms before age 45. Males are more commonly affected than females, who tend to be diagnosed later partly due to milder symptoms.

Diagnosis

Diagnostic criteria were established by the European Spondyloarthropathy Study Group in the early 1990s. A clinical diagnosis of AS requires the presence of spinal pain caused by inflammation or inflammation of the membrane surrounding the joints, which can be either asymmetric or involving primarily the lower limbs. One or more of the following conditions must also be present:

- Family history of AS
- Sacroilitis (inflammation of the sacroiliac joint) demonstrated by x ray
- Acute diarrhea within one month before the appearance of symptoms
- Inflammatory bowel disease
- Psoriasis (a scaly skin disease)
- Urethritis (inflammation of the urethra)
- Cervicitis (inflammation of the cervix)
- Alternating buttock pain
- Enthesopathy (disorder of the ligament attachment to the bone)

This diagnostic description has close to an 87% sensitivity, meaning that 87% of those with AS are picked up using this description. Conversely, 13% of those with AS will not be identified as having the disease based on this description. The description has a specificity that is also approximately 87%, meaning that 87% of the time a person classified as having AS actually has AS, as opposed to another disease or no disease. Conversely, about 13% of the time this description will incorrectly classify someone who actually has a different disease as having AS.

This is a challenging diagnosis to make correctly. Testing for HLA B-27 can improve diagnosis by confirming specificity. In other words, when it looks like someone has AS based on the above description of conditions, a positive B-27 test will make the physician more certain that person is a true positive for AS. As imaging of the sacroiliac joint improves through the use of a technology called *magnetic resonance imaging (MRI)*, diagnosis of AS may also improve. Although, diagnosing a person with AS prior to the development of signs seen on x ray or MRI will continue to be very difficult.

Treatment and management

Phyical therapy plays a major role in maintaining flexibility, range-of motion, posture, and ultimately mobility. Surgery can improve joint function, as well as minimize associated pain, which may be treated with nonsteroidal anti-inflammatory medications. Other medications—sulfasalazine and methotrexate—can provide some relief for peripheral arthritis. Cycloplegics (medications that paralyze the ciliary muscle of the eye) and local steroids are effective at treating anterior uveitis. Rare complications are treated depending on their symptoms. Avoidance of smoking is encouraged to maintain lung function.

Prognosis

For most affected individuals, treatment and management is successful at maintaining quality of life. Quality can be significantly impacted, however, for the occasional individual with a severe, progressive course of the disease. Vision can be affected in some individuals with anterior uveitis that is not responsive to treatment, but this is rare. The rare complication of kidney failure can limit life-expectancy, as can respiratory failure that may result from smoking.

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Jennifer Denise Bojanowski, MS, CGC

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Craniofacial—Relating to or involving both the head and the face.

Dermatologist—A physician that specializes in disorders of the skin.

Fontanelle—One of several "soft spots" on the skull where the developing bones of the skull have yet to fuse.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Mandible—Lower jaw bone.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Ophthalmologist—A physician specializing in the medical and surgical treatment of eye disorders.

Orthodontist—Dentist who specializes in the correction of misaligned teeth.

Otolaryngologist—Physician who specializes in the care of the ear, nose, and throat and their associated structures.

Psychologist—An individual who specializes in the science of the mind.

Sleep apnea—Temporary cessation of breathing while sleeping.

Speech therapist—Person who specializes in teaching simple exercises to improve speech.

Suture—"Seam" that joins two surfaces together.

Syndactyly—Webbing or fusion between the fingers or toes.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Anxiety neurosis *see* **Panic disorder**

Apert syndrome

Definition

Premature closure of the skull bones leading to facial distortion with an usually tall skull and fusion of the fingers and toes, known as syndactyly, are the major features of Apert syndrome (AS). Another name for this disorder is acrocephalysyndactyly.

Description

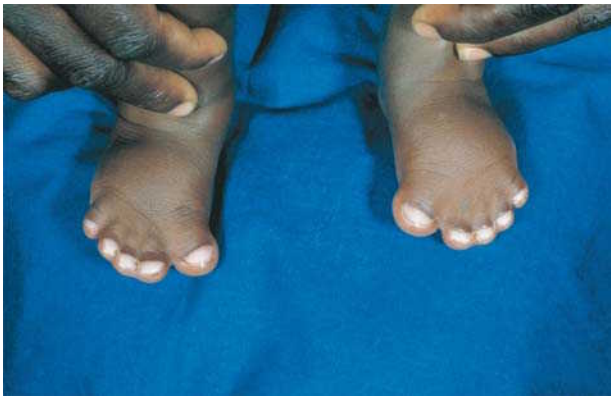
A French physician, E. Apert, first reported in 1906 the syndrome that bears his name. He detailed the skull malformation, midface hypoplasia (underdevelopment) and the hand abnormalities. The hand appears mitten-shaped because of the finger fusion. Intelligence varies from normal to severe mental retardation.

Genetic profile

Apert syndrome (AS) is an autosomal dominant disorder, meaning a person only has to inherit one non-working copy of the **gene** to manifest the condition. In most cases, AS is sporadic, meaning that the parents are usually unaffected but a fresh mutation or gene change occurring in the egg or sperm was passed onto the affected child. For these families the chance to have another affected child is very low. An affected parent has a 50% chance of passing on the abnormal gene to their child, who will then also have Apert syndrome.

Two unique mutations in the fibroblast growth factor receptor 2 (FGFR2) gene located on chromosome 10 were discovered in 1995. This gene directs the development of bone formation. When parental studies were performed, genetic researchers determined that the father passed on the gene causing AS and was usually older than 30 years. No explanation has been found for this unusual finding.

After comparing the physical findings with gene mutations causing AS, researchers noted that one muta-



Webbing of the feet is a characteristic sign of Apert syndrome. *(Custom Medical Stock Photo, Inc.)*

tion resulted in a much more improved facial appearance after corrective surgery. The other mutation produced a more severe form of syndactyly.

Demographics

Apert syndrome has been estimated to occur in one of every 60,000 to 160,000 births. All races and both sexes are equally affected.

Signs and symptoms

At birth the craniofacial (pertaining to the skull and face) appearance is striking. Early or premature closure of the skull sutures (layer of fibrous tissue connecting the skull bones) makes the skull grow taller than normal with a short distance from the front to the back of the head. Always it is the coronal suture connecting the frontal and parietal bones that fuses early. The buildup of pressure on the brain is minimal because the fontanelles, or soft spots, and midline of the skull remain open. Due to the small space within the eye sockets, the eyeballs bulge outwards and to the side. Also, the eyelids have a downward slant and cannot completely close.

From the middle of the eye sockets to the upper jaw, the face is sunken in or concave when viewed from the profile. This midfacial hypoplasia causes the upper jaw to slope backward pushing the lower teeth in front of the back teeth.

The mouth area has a prominent mandible (lower jaw), down-turned corners, high arched palate, cleft palate (an opening in the roof of the mouth), crowded upper teeth, poor contact between the upper and lower teeth, and delayed tooth eruption.

Syndactyly of the fingers and toes involves not only soft tissues but also the bones, nerves, and tendons. Flexing of the fingers and toes after the first digit is not usually possible. The thumb can be unattached or fused to the other fingers. Also, the other fingers may or may not be fused to each other in varying degrees. Fusion of the toes is less worrisome. Correction only becomes necessary when walking is difficult.

Most children with AS are noisy breathers. The nose and airways leading to the lungs are smaller than usual. These narrow passageways probably make breathing more difficult. At night if breathing is troublesome, sleep apnea can occur. This stoppage of breathing while sleeping deprives the brain and body of oxygen. Mental impairment can occur as a result of oxygen deprivation.

Excessive sweating is often seen. Researchers do not know why the sweat glands are overactive. As the children reach puberty, they develop excessive acne. A skin specialist or dermatologist can help to control it.

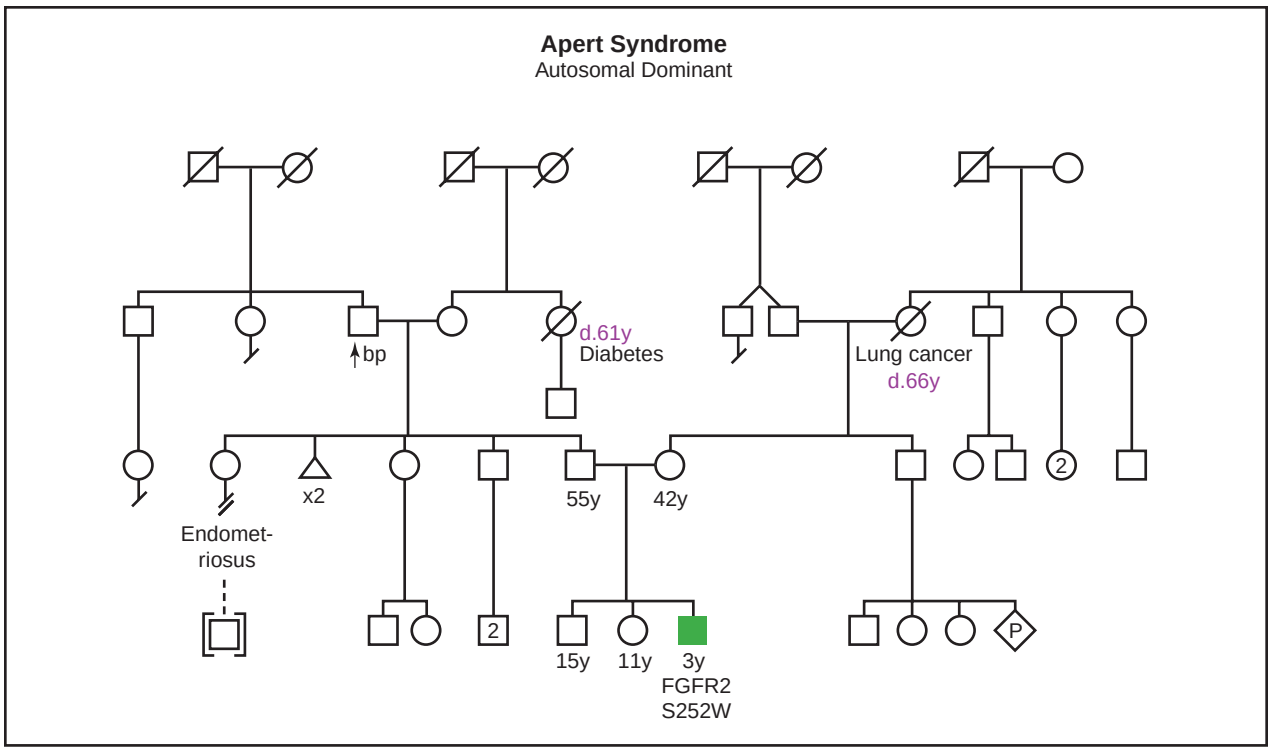
The height and weight of children with AS is usually normal. However, their learning ability can be affected. A small number of children with Apert syndrome will have a normal level of intelligence while the majority will have some degree of mental retardation.

Diagnosis

During the newborn period most babies will be diagnosed after a geneticist examines them. This doctor specializes in diagnosing and explaining hereditary conditions. The unusual facial features and hand syndactyly are unique to AS. Testing for the mutations known to cause AS should be arranged. If a mutation is found, then the diagnosis can be made. When a mutation is not found, the physical findings alone can support the diagnosis.

Occasionally during an ultrasound examination a fetus shows characteristics suggesting AS. This examination is best done after 16 weeks of pregnancy. Ultrasound is the use of sound waves to create a real time image of the fetus. Unlike x rays, ultrasound is not dangerous and the fetus can be examined for size, viability, and birth defects.

An experienced physician or ultrasound technician performing the examination may detect the caved in profile and syndactyly. More than one examination may be necessary to confirm the findings. If AS is suspected then **genetic testing** can be offered during the pregnancy. The pregnant woman can undergo an **amniocentesis** to obtain fetal cells that can be analyzed for the mutations causing AS. Amniocentesis is the removal of amniotic fluid that surrounds the fetus by a needle inserted through the uterus. Results may take as long as 4 weeks.



(Gale Group)

Treatment and management

The best treatment for AS begins at birth with the correct diagnosis. To provide better care, a craniofacial team should be involved. With the team approach all the specialists are in one center to minimize the number of appointments and corrective surgeries. More important, this team consists of specialists who understand the complex problems of AS and the family's concerns. Included on this team are a craniofacial surgeon, neurosurgeon, otolaryngologist (specialist of the ears, nose, and throat), ophthalmologist (eye specialist), orthodontist, speech therapist, and psychologist. A pediatric nurse, geneticist or genetic counselor, and social worker may also be part of the team during the first few years of the child's life. Many major medical centers will have a craniofacial team or the family can be referred to one.

Working together the craniofacial surgeon and neurosurgeon perform the multiple surgeries to reshape the tower skull. They reopen the prematurely closed sutures between the skull bones and then pull the front of the skull forward to create space within it and enlarge the eye orbits. Average age for these operations is about 4-8 months.

From ages five to nine the child will undergo a surgical procedure called a midface advancement. This technique will correct the concave profile that becomes pronounced because the upper and lower face grow normally while the middle of the face grows slowly. Corrective facial surgeries continue until the early adult years when growth is finally completed.

The neurosurgeon may perform the operations to unfuse and straighten the fingers. However, a completely normal hand cannot be created.

Frequent ear infections can decrease a child's hearing level. The otolaryngologist can monitor the hearing. Sometimes tiny plastic tubes are placed in the ears to prevent hearing loss from repeated infections.

The abnormal placement of the eyes and its muscles can sometimes prevent a child from looking straight ahead with both eyes. An ophthalmologist should examine the eyes regularly and correct a muscle imbalance of the eyes with surgery.

An orthodontist (dentist who specializes in correcting misaligned teeth) monitors the teeth because the abnormal jaw structure causes poor development and placement. An oral surgeon may correct the misalignment of the teeth. Proper positioning of the teeth improves speech and facial appearance.

Speech and language delay can result from decreased hearing and an unusual jaw shape. A speech

therapist works with the child to develop language skills through simple exercises.

The facial appearance of Apert syndrome can have a devastating emotional effect on the child and family. Support from a psychologist (a specialist in science of the mind) can help the child develop a positive self-image and help parents cope with feelings of guilt. Often parents will blame themselves for a child's condition even if they in no way caused it or could have prevented it. The multiple doctors' visits and surgeries can create undue stress as well.

During the many hospitalizations, a pediatric nurse will care for the child. This nurse has received specialized training in the treatment of children with craniofacial disorders. Also, the nurse may introduce the child to the hospital.

Diagnosis of Apert syndrome will usually be made by the geneticist. The family will discuss with the genetic counselor how AS is inherited and the chance for future children to be affected.

Having a child with AS can place a tremendous financial strain on the family. A social worker gives the family important information about medical coverage. This person can also help coordinate medical care and special education services.

Prognosis

Many factors affect the prognosis of a child with AS. The age at which the first surgery takes place to create spaces between the skull bones is important. Mental retardation can result from the buildup of pressure on the brain. Having a supportive, loving family environment increases the chances for normal development. Children with complex medical problems who lack a supportive setting often have delayed mental, social, and emotional development.

Although the hands will never be completely normal, surgeries to separate and straighten the fingers can be done. Tasks such as writing and manipulating buttons will be difficult. Adaptive devices in school and home will allow for more independence. Separation of the toes usually does not improve walking but may improve the child's self image.

Persons with AS who have a normal intelligence level can have full, productive lives. Vocational training will help those with borderline intelligence.

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Apert Syndrome Support Group. 8708 Kathy, St. Louis, MO 63126. (314) 965-3356.

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

FriendshipCenter.com. <http://www.friendshipcenter.com>.

Suzanne M. Carter, MS, CGC

Arginase deficiency

Definition

Arginase deficiency is an inborn error of metabolism that results from a defect in the urea cycle. This cycle is a series of biochemical reactions that occur in the body in order to remove ammonia from the bloodstream.

Description

During normal cellular function, proteins are broken down into nitrogen waste products and put into the blood

stream as ammonia. The urea cycle transforms this toxin into urea, which can be safely removed by the kidneys as urine. Lack of an enzyme from the urea cycle, such as arginase, can result in the buildup of toxins in the body. There are six diseases that belong in the group of urea cycle disorders. Arginase is thought to be the rarest of these disorders.

The enzyme arginase is the last step of the urea cycle, where it turns arginine into ornithine and urea. If a person is born with arginase deficiency then they build up arginine in their blood. This is called argininemia. Since earlier steps in the urea cycle are left intact, patients may or may not build up ammonia in the blood. Commonly, the build up of arginine presents as a central nervous system disease or developmental delay in young children.

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Urea cycle disorder—A disease caused by a lack of the enzyme that removes ammonia from blood.

Genetic profile

Arginase deficiency is an autosomal recessive trait. Thus, both parents of an affected child would have to be carriers of the **gene**. There are two genetically distinct arginases in the human body. The arginase that is expressed in the liver and in red blood cells is the one that is lost in arginase deficiency. This gene has been mapped to the long arm of chromosome 6, specifically 6q23. Twenty different mutations have been found in patients with the disease.

Demographics

Like other autosomal recessive diseases, arginase deficiency remains rare. The first signs of this disease tend to occur while the patient is still very young. A child may have a normal birth, infancy, and may not show any signs of the disease for quite a few years. There is no gender or racial difference (men and women are both as likely to have the disease), but its absolute incidence rate cannot be known, due its rarity and the lack of statistics. Its incidence is well below one per 200,000.

Signs and symptoms

The onset of this disease tends to be subtle. While the first symptoms of this disease show up while the patient is still a baby, some infants are said to be normal before beginning to have the symptoms. In many cases, the disease is not found at first, and the child is labeled as having ‘cerebral palsy’ (a general term for neurologic problems that result in altered development—often starting at birth). The symptoms include: loss of normal developmental milestones (the child does not perform tasks at the usual age—walking and speaking, for example); poor feeding; not being able to eat proteins (i.e. a high protein meal makes symptoms worse); fussy behavior; lessened alertness; choreoathetotic movements (strange, uncontrollable writhing movements of limbs); spasticity of lower limbs (weakness and stiffness of legs); incoordination; tremors; seizures; and mental retardation. Affected children may also have an enlarged liver from the buildup of toxins.

Diagnosis

Diagnosis is made after children present with symptoms. The illness should be thought for children who have both a developmental delay and stiffness of the ankles and legs that interfere with walking. It should also be thought of anytime that other urea cycle disorders are considered. The lab test of choice is to measure arginase activity in red blood cells. If patients are truly deficient then they will have below normal activity levels. In patients in which there is a high chance of disease and only mildly elevated levels of arginine in the blood, more testing should be done. In other urea cycle disorders, patients tend to have hyperammonemia (a high amount of ammonia in the blood), but in arginase deficiency the ammonia levels are rarely raised. No prenatal diagnosis is currently done. If patients have one child with this disease, then they can be counseled about risk of disease in future children. Since this disease is inherited in an autosomal recessive pattern, each time carrier parents have a child there is a 25% chance that they will have an affected child.

Treatment and management

Treatment of arginase deficiency is similar to treatment methods for other urea cycle disorders. One would want to decrease, as much as one could, the amount of arginine that is building up. This is done through control of protein intake in foods. Arginine is one of the twenty amino acids that make up proteins, and if its intake is stopped, then the amount that can build up in a patient will be lessened. Supplements of essential amino acids (amino acids that cannot be made by the body and must

be obtained through food) are given so that children do not become ill from malnourishment.

Other symptoms can also be controlled. For example, patients who have seizures should be treated with an anti-seizure medication. Also, physical therapy can be helpful for patients with stiff legs and problems walking.

Prognosis

The long-term effects of arginase deficiency are better than that for other urea cycle disorders. With proper food intake, children can have much milder symptoms. Often, though, the disease is not found until after severe problems have occurred. Data about patients that live until they are adults is limited, but many cases of patients living through teenage years have been reported. Hence, prognosis is clearly related to how early the disease can be found. This means that it is a very good idea for children to get tested when this group of symptoms are present.

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Benjamin M. Greenberg

Arginiemia *see* **Arginase deficiency**

Arnold-Chiari malformation

Definition

Arnold-Chiari malformation is a rare genetic disorder. In this syndrome, some parts of the brain are formed abnormally. Malformations may occur in the lower portion of the brain (cerebellum) or in the brain stem. As of 2001, doctors are not sure of the cause of Arnold-Chiari malformation.

Description

A German pathologist named Chiari was the first to describe Arnold-Chiari malformation in 1891. Normally, the brain stem and cerebellum are located in the posterior fossa, an area at the base of the skull attached to the spinal cord. In Arnold-Chiari malformation, the posterior fossa does not form properly. Because the posterior fossa is small, the brain stem, cerebellum, or cerebellar brain tissues (called the cerebellar tonsils) are squeezed downward through an opening at the bottom of the skull. The cerebellum and/or the brain stem may extend beyond the skull or protrude into the spinal column. The displaced tissues may obstruct the flow of cerebrospinal fluid (CSF), the substance that flows around the brain and spinal cord. CSF nourishes the brain and spinal cord.

Although this malformation is present at birth, there may not be any symptoms of a problem until adulthood. For this reason, Arnold-Chiari malformation is often not diagnosed until adulthood. Women have a higher incidence of this disorder than men.

Other names for Arnold-Chiari malformation are Chiari malformation, Arnold Chiari syndrome, herniation of the cerebellar tonsils, and cerebellomedullary malformation syndrome. When doctors diagnose Arnold-Chiari malformation, they classify the malformation by its severity. An Arnold-Chiari I malformation is the least severe. In an Arnold-Chiari I malformation, the brain extends into the spinal canal. Doctors measure the length of brain stem located in the spinal canal to further define the malformation.

An Arnold-Chiari II malformation is more severe than an Arnold-Chiari I. It is almost always linked with a type of **spina bifida**. A sac protrudes through an abnormal opening in the spinal column. The sac is called a myelomeningocele. It may be filled with part of the spinal cord, spinal membranes, or spinal fluid. Unlike many cases of Arnold-Chiari I malformation, Arnold-Chiari II malformation is diagnosed in childhood. Doctors have identified Arnold-Chiari III and IV malformations, but they are very rare.

Arnold-Chiari malformations may occur with other conditions. There may be excessive fluid in the brain (**hydrocephalus**), opening in the spine (spina bifida), or excessive fluid in the spinal cord (syringomyelia), but many people with Arnold-Chiari malformations do not have other medical problems.

Genetic profile

As of 2001, doctors had not yet found the **gene** responsible for Arnold-Chiari malformations. There has not yet been a study that shows whether or not this disorder is inherited, but there are reports of several families where more than one family member has a Arnold-Chiari malformation.

Scientists do not know what causes Arnold-Chiari malformations. One hypothesis is that the base of the skull is too small, forcing the cerebellum downward. Another theory focuses on overgrowth in the cerebellar region. The overgrowth pushes the cerebellum downward into the spinal canal.

Demographics

Arnold-Chiari malformations are rare. As of 2001, there is no data that shows the incidence of Arnold-Chiari malformations. Arnold-Chiari malformations are the most common type of malformation of the cervico-medullary junction, the area where the brain and spine connect. About one percent of live newborns have a malformation in the cervico-medullary junction.

Signs and symptoms

Some people with Arnold-Chiari I malformations have no symptoms. Typically, with an Arnold-Chiari I malformation symptoms appear as the person reaches the third or fourth decade of life. Symptoms of this disorder vary. Most symptoms arise from the pressure on the cranial nerves or brain stem. The symptoms may be vague or they may resemble symptoms of other medical problems, so diagnosis may be delayed.

One of the most common symptoms of Arnold-Chiari malformations is a headache. The headache generally begins in the neck or base of the skull and may radiate through the back of the head. Coughing, sneezing, or bending forward may bring on these headaches. The headaches can last minutes or hours and may be linked with nausea.

There may be pain in the neck or upper arm with Arnold-Chiari malformations. Patients often report more pain on one side, rather than equal pain on both sides. There may also be weakness in the arm or hand. Patients may also report tingling, burning, numbness, or pins and needles. Balance can be affected as well. A person may be unsteady on their feet or lean to one side.

Some people with Arnold-Chiari malformation may have difficulty swallowing. They may say that food 'catches' in their throat when they swallow. Another common complaint linked with Arnold-Chiari malformations is hoarseness.

KEY TERMS

Cerebrospinal fluid—Fluid that circulates throughout the cerebral ventricles and around the spinal cord within the spinal canal.

Cervico-medullary junction—The area where the brain and spine connect.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Magnetic Resonance Imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Myelomeningocele—A sac that protrudes through an abnormal opening in the spinal column.

Posterior fossa—Area at the base of the skull attached to the spinal cord.

Spina bifida—An opening in the spine.

Syringomyelia—Excessive fluid in the spinal cord.

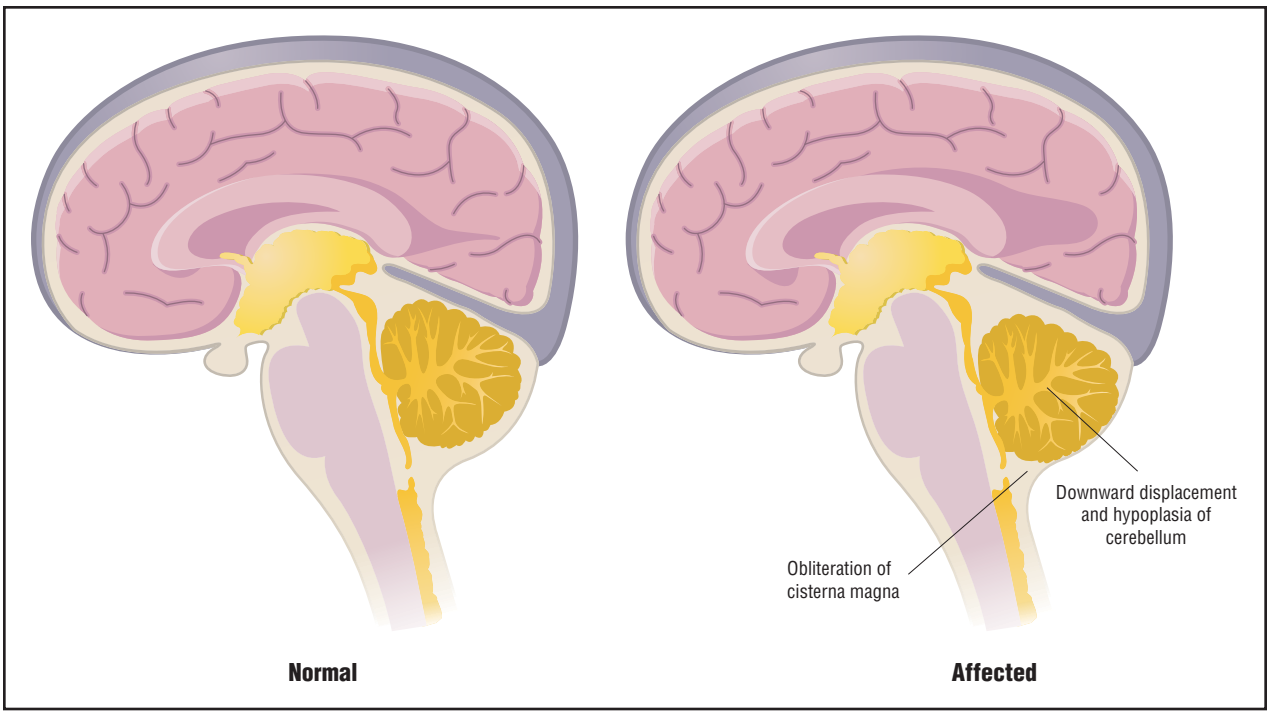
People with Arnold-Chiari malformations may have visual problems, including blurred vision, double vision, or blind spots. There may be bobbing of the eyes.

Diagnosis

A Arnold-Chiari malformation is diagnosed with magnetic resonance imaging (MRI). An MRI uses magnetism and radio waves to produce a picture of the brain and show the crowding of the space between the brain and spinal cord that occurs with Arnold-Chiari malformations. In addition to an MRI, patients will also have a thorough neurologic examination.

Treatment and management

The recommended treatment for an Arnold-Chiari I malformation is surgery to relieve the pressure on the cerebellar area. During the surgery, the surgeon removes a small part of the bone at the base of skull. This enlarges and decompresses the posterior fossa. This opening is patched with a piece of natural tissue. In some people with Arnold-Chiari malformation, displaced brain tissue affects the flow of cerebrospinal fluid. Doctors may evaluate the flow of cerebrospinal fluid during surgery for Arnold-Chiari malformation. If they find that brain tissue is blocking the flow of cerebrospinal fluid, they will shrink the brain tissue during surgery.



A characteristic change that occurs in patients with Arnold-Chiari syndrome, type II, is the downward positioning of the cerebellum. This displacement destroys the area of the cisterna magna. *(Gale Group)*

Prognosis

Long-term prognosis for persons with Arnold-Chiari I malformations is excellent. Full recovery from surgery may take several months, during that time, patients may continue to experience some of the symptoms associated with Arnold-Chiari malformations. Prognosis for Arnold-Chiari II malformations depends on the severity of the myelomeningocele and will be equivalent to that of spina bifida.

Resources

ORGANIZATIONS

American Syringomelia Project. PO Box 1586, Longview, Texas 75606-1586. (903)236-7079.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. ((203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.raredisease.org>.

World Arnold-Chiari Malformation Association. 31 Newton Woods Road, Newton Square, Philadelphia, PA19073. <http://presenter.com?~wacma/milhorat.htm>.

Lisa A. Fratt

Arteriohepatic dysplasia (AHD) *see* **Alagille syndrome**

Arthrogryposis multiplex congenita

Definition

Arthrogryposis multiplex congenita (AMC) is a term used to describe the presence of two or more (multiplex) joint contractures (arthrogryposis) present at birth (congenita). A joint contracture is a limitation of the normal range of motion of a joint.

Description

There are at least 21 recognized forms of AMC. Ten of these fall into a category called the distal arthrogryposes. Four of these are syndromes that include AMC as a set of symptoms. Each involves at least two joint contractures evident from birth. None of the AMC disorders are progressive, meaning the symptoms do not worsen with age.

Distal arthrogryposes (DAs) are all characterized by contractures of the fingers and toes. Each type can be distinguished by specific characteristics:

- Type 1a DA: club feet that point inward and down (talipes equinovarus).
- Type 2 DA: down slanting of the opening between the upper and lower eyelids (palpebral fissures), a small

mouth with pursed lips and malformations of the nose that cause a whistling appearance upon breathing, a curvature of the spine (**scoliosis**), and some instances of mild developmental retardation. Type 2b DA, is characterized by those characteristics of type 2 DA accompanied by earlobes that are attached to the skin of the face and a permanent bending (flexion) of one or more fingers (camptodactyly).

- Type 3 DA: talipes equinovarus, camptodactyly, short stature, and vertebral abnormalities.
- Type 4 DA: short stature, an abnormally short neck, immobile facial expressions, camptodactyly, and the lack of the normal prominent creases (flexion creases) on the palms of the hands.
- Type 5 DA: contractures of the arms and legs, limited eye movement, deep set eyes, and abnormal coloring of the retina of the eye.
- Type 6 DA: camptodactyly, an abnormally small head (microcephaly), and hearing loss caused by an abnormality of the auditory nerve (sensorineural hearing loss).
- Type 7 DA: camptodactyly when an affected individual attempts to open the hand, short stature, abnormally short muscles in the legs, and an inability to open the mouth completely (trismus).
- Type 8 DA: contractures of the wrist and/or ankles, short stature, and scoliosis.
- Type 9 DA: lack of muscle tone and development, abnormally low shoulder-to-shoulder width to body height ratio (marfanoid habitus), severe outward curvature of the spine in the neck and upper back (kyphoscoliosis), and contractures of the hips and shoulders.

The most serious forms of DA are types 6 and 9.

Signs and symptoms

The four syndromes that include arthrogryposis as a set of symptoms are cerebrooculofacioskeletal syndrome, adducted thumb-clubfoot syndrome, **Saethre-Chotzen syndrome**, and arthropathy-camptodactyly-pericarditis syndrome. Cerebrooculofacioskeletal (COFS) syndrome is characterized by an abnormally small head (microcephaly), a lack of muscle tone (hypotonia), eye defects, abnormally large ears and nose, a receding chin (micrognathia), and kyphoscoliosis. Adducted thumb-clubfoot syndrome is characterized by **clubfoot** (equinovarus talipes), clasped (adducted) thumbs, abnormally long fingers and toes (arachnodactyly), a prominent forehead, and psychomotor delay. Saethre-Chotzen syndrome is characterized by flattened facial features, wide set eyes (hypertelorism), abnormalities of the skull (**craniosyno-**

KEY TERMS

Amniotic fluid—The fluid which surrounds a developing baby during pregnancy.

Amyoplasia—The mildest form of arthrogryposis muliplex congenita, characterized by sporadic and recurrent contractures of the wrists, elbows, and knees; club feet, and an abnormal internal rotation of the shoulders.

Arthrogryposis—Abnormal joint contracture.

Camptodactyly—An abnormal permanent bending of one or more fingers or toes.

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Distal arthrogryposis—A disorder characterized by contractions of the muscles in the hands.

Flexion—The act of bending or condition of being bent.

Flexion creases—The lines present on the palms of the hands and the soles of the feet from normal bending of these body parts. Some individuals affected with arthrogryposis lack these characteristic lines.

Inheritance pattern—The way in which a genetic disease is passed on in a family.

Marfanoid habitus—An abnormally low weight to height ratio that is sometimes seen in extremely tall and thin people.

Neurologic—Pertaining the nervous system.

Palpebral fissures—The opening between the upper and lower eyelids.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Talipes equinovarus—A type of clubfoot characterized by a downward and inward pointing foot.

Trisomy 18—A chromosomal alteration where a child is born with three copies of chromosome number 18 and as a result is affected with multiple birth defects and mental retardation.

Ultrasound evaluation—A procedure which examines the tissue and bone structures of an individual or a developing baby.

stosis), abnormalities of the eyes, partially fused fingers or toes (syndactyly), **congenital heart defects**, and contractures of the elbows and knees. Arthropathy-camptodactyly-pericarditis syndrome is characterized by contractures of the elbows, wrists, and fingers; an abnormally elevated generalized stiffness upon waking; arthritis of the hips, shoulders, elbows, and knees; and, inflammation of the membranous sac that protects the heart (pericarditis).

The other forms of AMC include three relatively common forms: X-linked arthrogryposis, neurogenic arthrogryposis, amyoplasia; and four extremely rare forms that may or may not represent distinct disorders: spondylospinal thoracic dysostosis, Jarcho-Levin syndrome, prenatal growth retardation with pelvic hypolasia and arthrogryposis in the lower limbs, and lethal congenital contracture syndrome.

X-linked arthrogryposis is generally mild and affects only the legs. Neurogenic arthrogryposis is also relatively mild and affects only the elbows and the knees. Amyoplasia is the mildest form of arthrogryposis; it is generally sporadic in appearance. Amyoplasia is characterized by contractures of the wrists, elbows, and knees; club feet, and an abnormal internal rotation of the shoulders.

Spondylospinal thoracic dysostosis is characterized by a short, curved spine; a short neck; malformations of the bones of the mouth; abnormal ribs; and congenital heart defects. Jarcho-Levin syndrome is characterized by many of the same characteristics of spondylospinal thoracic dysostosis. These two disorders differ only in the presence of a fusion of certain spinal vertebrae in spondylospinal thoracic dysostosis that has not been observed in Jarcho-Levin syndrome. Prenatal growth retardation with pelvic hypoplasia and arthrogryposis in the lower limbs has only been described in a pair of sisters and four males and one female, all of whom were siblings. It seems likely that this disorder is one of the distal arthrogryposes. Lethal congenital contracture syndrome almost inevitably leads to prenatal death prior to week 32 of gestation. It appears to be a unique variant of AMC.

Genetic profile

Various forms of arthrogryposis have been traced to a variety of gene mutations. Type 1a DA has been linked as a non-sex linked (autosomal) dominant trait caused by a mutation on the short arm of chromosome 9 at location 9p21-q21. Type 2 DA has not been localized to a particular chromosome and it is not clear how this disorder is transmitted. Type 2b DA has been linked to an autosomal dominant trait caused by a mutation on a gene localized to the short arm of chromosome 11, specifically 11p15.5. Types 3, 4, 5, 6, 7, and 8 DA have also not been localized to specific genes, but are presumed to be autosomal dominant traits. Type 8 DA may also be transmitted as a recessive or an X-linked disorder. Type 9 DA has been linked to an autosomal dominant gene on the long arm of chromosome 5, localized to 5q23-q31.

Cerebrooculofacioskeletal syndrome is an autosomal recessive trait caused by a mutation on a gene that has been localized to the long arm of chromosome 10, 10q11 specifically. Adducted thumb-clubfoot syndrome has DA that has not been localized to a particular chromosome but it is transmitted through a recessive trait. Saethre-Chotzen syndrome has been linked to an autosomal dominant trait caused by a mutation in the TWIST gene that has been localized to 7p21 on the short arm of chromosome 7. Arthropathy-camptodactyly-pericarditis syndrome has been linked to an autosomal recessive trait caused by a mutation on a gene that has been localized to the long arm of chromosome 1 at 1q25-q31.

X-linked arthrogryposis is an X-linked trait caused by a mutation on a gene that has been localized to Xp11.3-p11.2. Neurogenic arthrogryposis has been linked to both an X-linked trait and a trait caused by a gene mutation on the long arm of chromosome 5. Amyoplasia is usually sporadic and any genetic cause of this type of arthrogryposis is in doubt though vascular disruptions have been postulated. A genetic cause of spondylospinal thoracic dysostosis has not been identified. Jarcho-Levin syndrome has been linked to an autosomal recessive trait caused by a gene mutation on chromosome 19, localized to 19q13. Lethal congenital contracture syndrome has been linked to an autosomal recessive trait caused by a mutation on a gene localized to 9q34 on chromosome 9.

Demographics

Arthrogryposis occurs in approximately one in every 3,000 live births. Most cases of arthrogryposis are caused by a lack of normal joint movement during fetal development. For this reason, cases of non-genetic arthrogryposis are more frequent in multiple birth pregnancies than in single birth pregnancies. Most forms of arthrogryposis are not known to affect one subpopulation more than another. However, Jarcho-Levin syndrome has been found almost exclusively in Puerto Ricans. All forms of AMC appear to affect males with approximately twice the frequency seen in females.

Diagnosis

The symptoms of AMC are primarily immobility of two or more joints. The most common joints affected are the joints of the fingers and toes. Less commonly affected

joints are the knees and elbows, and rarely affected joints are the jaws, hips and shoulders.

A diagnosis of AMC is indicated by the presence of two or more joint contractures present from birth. The symptoms that are present allow the differential diagnosis between one of the forms of distal arthrogryposis, a syndromic form of arthrogryposis, and the other forms of arthrogryposis.

Treatment and management

Physical therapy has proven an effective treatment for almost all froms of AMC. Splints, braces, and removable casts are often used to improve joint positioning. In most cases, these orthopedic devices are used only at night so that proper joint mobility can be encouraged during the waking hours.

Occassionally, surgery to repair foot and ankle position may be necessary, especially in the case of talipes equinovarus. Much less frequently, orthopedic surgery of the hips, kness, elbows, shoulders, and wrists is required. Tendon replacement surgery has also been successful in individuals affected with AMC.

In an informal Internet study on AMC and aging conducted in 2000, one-third of the 100 respondents replied that they had sought alternative therapies for symptoms related to AMC. The most common of these therapies being massage therapy, hydrotherapy, and acupuncture. Massage therapy was reported as providing excellent results for some, but the lack of medical coverage for these therapies combined with their cost prevented many from continuing these treatments. When asked what helped the most in relieving symptoms of AMC, 44% of respondents named pain or anti-inflammatory drugs, both prescription and over-the-counter types. Another 20% mentioned massage, and 18% mentioned heat treatments such as saunas, hot tubs, hot packs, or hot showers and/or baths. Most survey participants noted that if they decreased their physical activity, they felt a loss of both joint mobility and stamina.

Prognosis

In cases of AMC that do not involve complications of the central nervous system, the outlook is quite good. Most individuals can achieve a sufficient range of motion in their affected joints to live healthy, complete lives. AMC is non-progressive, therefore, once a joint contracture has been repaired through physical therapy and/or surgery, it will generally not return to a state of abnormal contracture.

When AMC is complicated by involvement of the central nervous system, approximately half of affected individuals die in infancy. Among the surviving half, many have varying degrees of mental retardation.

The informal Internet survey on AMC and aging conducted in 2000, found that 50% of the 100 respondents could walk without assistance. Twenty-five percent needed braces, canes, and/or crutches, while the remaining 25% used either a scooter or wheelchair. The number of people requiring assistance to walk is expected to decline over time since many of those individuals responding to this survey did not receive medical and physical therapy treatments that are now routinely available to children affected with AMC.

Two-thirds of these survey respondents also stated that they had arthritis or arthritis-like symptoms. An informal causal relationship was also made between those who had rigorous or painful childhood physical therapy and later suffered symptoms of arthritis.

Resources

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ORGANIZATIONS

Arthrogryposis Group (TAG). 1 The Oaks, Gillingham, Dorset, SP8 4SW. UK 01-747-822655. <http://tagonline.org.uk>.

AVENUES National Support Group for Arthrogryposis Multiplex Congenita. PO Box 5192, Sonora, CA 95370. (209) 928-3688. avenues@sonnet.com. <http://www.sonnet.com/avenues>.

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Paul A. Johnson

KEY TERMS

Allele—One of two or more alternate forms of a gene.

Arthropathy—Any disease or disorder that affects joints.

Camptodactyly—A condition characterized by the bending of one or more fingers.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Congenital disorder—Refers to a disorder which is present at birth.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Haplotype—The set of alleles on one chromosome.

Locus—The physical location of a gene on a chromosome.

Arthropathy-camptodactyly syndrome

Definition

Arthropathy-camptodactyly syndrome is a disorder affecting the joints of the fingers. Arthropathy refers to a disease or disorder affecting a joint, and camptodactyly is a congenital condition, meaning present at birth, characterized by the bending of one or more fingers.

Description

In people with arthropathy-camptodactyly syndrome, one or more fingers are bent. Other joints may be affected as well—some children with arthropathy-camptodactyly syndrome also have swollen knees and ankles, and hip pain.

Problems with the pericardium, the sac that surrounds the heart, are also common in children with arthropathy-camptodactyly syndrome. In many cases the pericardium is removed, a surgical procedure called pericardiectomy.

Genetic profile

Arthropathy-camptodactyly syndrome typically occurs in children (both male and female) whose parents are related by blood. In one case, it was determined that the parents of children with arthropathy-camptodactyly syndrome shared the haplotype A1-Bw21. The gene map locus 1q24-q25 is also implicated.

Demographics

As of 2000, cases of arthropathy-camptodactyly syndrome have been diagnosed in Canada, India, Mexico, Newfoundland, Pakistan, Saudi Arabia, and Turkey, as well as in African Americans.

Signs and symptoms

People with arthropathy-camptodactyly syndrome have a bend in the joint of one or more fingers. Other symptoms include swollen knees and ankles, and hip pain.

Inflammation of the sac lining the heart (pericarditis) is another observed symptom, often accompanied by chest pain. The pain is usually sharp, and felt behind the breast bone (sternum).

Diagnosis

Aside from the physical observation of bent fingers, no test is presently available to confirm diagnosis.

Treatment and management

Surgery can correct the bent fingers disorder that characterizes arthropathy-camptodactyly syndrome. Removal of the tendon sheaths in the affected fingers can help to keep them mobile. Removal of the membranes surrounding a joint (synovectomy) of other body joints, such as knees, can also help maintain mobility.

In at least one case, a bent finger straightened without intervention.

Pericardiectomy is often performed to relieve the pericarditis often associated with the disorder.

Prognosis

As of 2000, case studies show that children with arthropathy-camptodactyly syndrome have lived into their teens. There is reason to believe that with the proper treatment, the disorder is not life-shortening.

Resources

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Sonya Kunkle

Asperger syndrome

Definition

Asperger syndrome (AS), which is also called Asperger disorder or autistic psychopathy, belongs to a group of childhood disorders known as pervasive developmental disorders (PDDs) or autistic spectrum disorders. AS was first described by Hans Asperger, an Austrian psychiatrist, in 1944. Asperger's work was unavailable in English before the mid-1970s; as a result, AS was often unrecognized in English-speaking countries until the late 1980s. Before the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV 1994), there was no official definition of AS.

KEY TERMS

Autistic psychopathy—Hans Asperger's original name for Asperger syndrome. It is still used occasionally as a synonym for the disorder.

Gillberg's criteria—A six-item checklist for Asperger syndrome developed by Christopher Gillberg, a Swedish researcher. It is widely used as a diagnostic tool.

High-functioning autism (HFA)—A subcategory of autistic disorder consisting of children diagnosed with IQs of 70 or higher.

Nonverbal Learning Disability (NLD)—A learning disability syndrome identified in 1989 that may overlap with some of the symptoms of Asperger syndrome.

Pervasive developmental disorder (PDD)—The term used by the American Psychiatric Association for individuals who meet some but not all of the criteria for autism.

Description

Children with AS learn to talk at the usual age and often have above-average verbal skills. They have normal or above-normal intelligence and the ability to take care of themselves. The distinguishing features of AS are problems with social interaction, particularly reciprocating and empathizing with the feelings of others; difficulties with nonverbal communication (e.g., facial expressions); peculiar speech habits that include repeated words or phrases and a flat, emotionless vocal tone; an apparent lack of "common sense"; a fascination with obscure or limited subjects (e.g., doorknobs, railroad schedules, astronomical data, etc.) often to the exclusion of other interests; clumsy and awkward physical movements; and odd or eccentric behaviors (hand wringing or finger flapping; swaying or other repetitious whole-body movements; watching spinning objects for long periods of time).

Genetic profile

There is some indication that AS runs in families, particularly in families with histories of **depression** and **bipolar disorder**. Asperger noted that his initial group of patients had fathers with AS symptoms. Knowledge of the genetic profile of the disorder, however, is quite limited as of 2001.

Demographics

Although the incidence of AS has been variously estimated between 0.024% and 0.36% of the general population in North America and northern Europe, further research is required to determine its true rate of occurrence—especially because the diagnostic criteria have been defined so recently. In addition, no research regarding the incidence of AS has been done on the populations of developing countries.

AS appears to be much more common in boys. One Swedish study found the male/female ratio to be 4:1. Dr. Asperger's first patients were all boys, but girls have been diagnosed with AS since the 1980s.

Signs and symptoms

About 50% of patients with Asperger syndrome have a history of oxygen deprivation during the birth process, which has led to the hypothesis that the syndrome is caused by damage to brain tissue before or during childbirth. Another cause that has been suggested is an organic defect in the functioning of the brain. Behavioral symptoms that are considered diagnostically significant are described in the next section.

Diagnosis

As of 2001, there are no blood tests or brain scans that can be used to diagnose AS. Until DSM-IV (1994), there was no "official" list of symptoms for the disorder, which made its diagnosis both difficult and inexact. Although most children with AS are diagnosed between five and nine years of age, many are not diagnosed until adulthood. Misdiagnoses are common; AS has been confused with such other neurological disorders as Tourette's syndrome, or with Attention-Deficit Disorder (ADD), Oppositional Defiant Disorder (ODD), or Obsessive-Compulsive Disorder (OCD). Some researchers think that AS overlaps with some types of learning disability, such as the Nonverbal Learning Disability (NLD) syndrome identified in 1989.

The inclusion of AS as a separate diagnostic category in DSM-IV was justified on the basis of a large international field trial of over a thousand children and adolescents. Nevertheless, the diagnosis of AS is also complicated by confusion with such other diagnostic categories as "high-functioning (IQ >70) autism," or HFA, and "schizoid personality disorder of childhood." With regard to the latter, AS is not an unchanging set of personality traits but has a developmental dimension. AS is distinguished from HFA by the following characteristics:

- Later onset of symptoms (usually around three years of age)
- Early development of grammatical speech; the AS child's verbal IQ is usually higher than performance IQ (the reverse being the case in autistic children)
- Less severe deficiencies in social and communication skills
- Presence of intense interest in one or two topics
- Physical clumsiness and lack of coordination
- Family is more likely to have a history of the disorder
- Lower frequency of neurological disorders
- More positive outcome in later life.

DSM-IV criteria for Asperger syndrome

DSM-IV specifies six diagnostic criteria for AS:

- The child's social interactions are impaired in at least two of the following ways: markedly limited use of nonverbal communication; lack of age-appropriate peer relationships; failure to share enjoyment, interests, or accomplishment with others; lack of reciprocity in social interactions.
- The child's behavior, interests, and activities are characterized by repetitive or rigid patterns, such as an abnormal preoccupation with one or two topics, or with parts of objects; repetitive physical movements; or rigid insistence on certain routines and rituals.
- The patient's social, occupational, or educational functioning is significantly impaired.
- The child has normal age-appropriate language skills.
- The child has normal age-appropriate cognitive skills, self-help abilities, and curiosity about the environment.
- The child does not meet criteria for another specific PDD or schizophrenia.

Other diagnostic scales and checklists

Other instruments that have been used to identify children with AS include Gillberg's criteria, a six-item list compiled by a Swedish researcher that specifies problems in social interaction, a preoccupying narrow interest, forcing routines and interests on the self or others, speech and language problems, nonverbal communication problems, and physical clumsiness; and the Australian Scale for Asperger Syndrome, a detailed multi-item questionnaire developed in 1996.

Brain imaging findings

As of 2001, only a few structural abnormalities of the brain have been linked to AS. Findings include abnormally large folds in the brain tissue in the left frontal region, abnormally small folds in the operculum (a lid-

like structure composed of portions of three adjoining brain lobes), and damage to the left temporal lobe. The first single photon emission tomography (SPECT) study of a patient found lower than normal blood supply in the left parietal area of the brain. Brain imaging studies on a larger sample of patients with AS is the next stage of research.

Treatment and management

As of 2001, there is no cure for AS and no prescribed regimen for all affected patients. Specific treatments are based on the individual's symptom pattern.

Medications

The drugs that are recommended most often for children with AS include psychostimulants (methylphenidate, pemoline), clonidine, or one of the tricyclic antidepressants (TCAs) for hyperactivity or inattention; beta blockers, neuroleptics, or lithium for anger or aggression; selective serotonin reuptake inhibitors (SSRIs) or TCAs for rituals and preoccupations; and SSRIs or TCAs for anxiety symptoms. One alternative herbal remedy that has been tried with some patients is St. John's wort.

Psychotherapy

Individuals with Asperger syndrome often benefit from psychotherapy, particularly during adolescence, in order to cope with depression and other painful feelings related to their social difficulties.

Educational considerations

Most patients with AS have normal or above-normal intelligence, and are able to complete their education up through the graduate or professional school level. Many are unusually skilled in music or good in subjects requiring rote memorization. On the other hand, the verbal skills of children with AS frequently cause difficulties with teachers, who may not understand why these "bright" children have social and communication problems. Some children are dyslexic; others have difficulty with writing or mathematics. In some cases, children with AS have been mistakenly put in special programs either for children with much lower levels of functioning, or for children with conduct disorders. Children with AS do best in structured learning situations in which they learn problem-solving and life skills as well as academic subjects. They frequently need protection from the teasing and bullying of other children, and often become hypersensitive to criticism by their teenage years.

Employment

Adults with AS are productively employed in a wide variety of fields. They do best, however, in jobs with regular routines or jobs that allow them to work in isolation. Employers and colleagues may need some information about Asperger syndrome in order to understand the employee's behavior.

Prognosis

AS is a lifelong but stable condition. The prognosis for children with AS is generally good as far as intellectual development is concerned, although few school districts as of 2001 are equipped to meet their special social needs. In addition, some researchers think that people with AS have an increased risk of becoming psychotic in adolscence or adult life.

Resources

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Families of Adults Afflicted with Asperger's Syndrome (FAAAS). PO Box 514, Centerville, MA 02632. <http://www.faaas.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Rebecca J. Frey, PhD

Asplenia

Definition

The term "asplenia" literally means absent spleen. However, in the condition asplenia, the spleen is not always absent. Sometimes the spleen is present, but not fully developed (hypoplastic). In asplenia, the spleen is typically not the only organ affected. Individuals with this condition often have problems with other organs and organ systems. A related condition is polysplenia. The term "polysplenia" literally means multiple spleens. Both of these conditions affect the placement and development of the organs inside the body. There is controversy over whether asplenia and the other syndromes, like polysplenia, that affect the position of the internal organs are actually different aspects of the same condition, referred to as Heterotaxy syndrome, or separate and distinct syndromes. As of 2001, this issue has not been resolved.

Asplenia is just one of the names used to refer to this condition. Other names include Ivemark syndrome, right isomerism sequence, bilateral right-sideness sequence, splenic agenesis syndrome, and asplenia with cardiovascular anomalies.

Description

The human body can be viewed as having a right side and a left side. Normally, inside the human body, the right side and the left side are different with respect to the presence of certain organs. Several organs inside the body are placed asymmetrically, meaning that one organ may be located on one side of the body, but not the other. Furthermore, there are some organs that are found on both sides of the body, but have differences that distinguish the right organ from its partner on the left side. In asplenia, the position, location, appearance, and performance of some of the internal organs are altered. Organs can often be found on the wrong side of the body and/or have structural defects. Furthermore, in most people the right and left organs are different; in people with asplenia, both organs may appear to be structured the same.

Genetic profile

In most families, asplenia is believed to occur sporadically. In other words, it occurs for the first time in a family and has no known or identifiable pattern of **inheritance**.

There have been several couples described in the medical literature who have more than one child diagnosed with asplenia. In several of these families, the parents were related to each other. Individuals who are related to each other are more likely to carry some of the same non-working genes. Therefore, these families illustrate the possibility that asplenia can be inherited in an autosomal recessive manner. Individuals who have an autosomal recessive condition have both genes in a pair that do not work as expected or are missing, thereby causing the disease. One non-working **gene** is inherited from the mother and the other is inherited from the father. These parents are called carriers of that condition. When two people are known carriers for an autosomal recessive condition, they have a 25% chance with each pregnancy of having a child affected with the disease.

There are a few families where asplenia appears to be inherited in an autosomal dominant or X-linked manner. In autosomal dominant inheritance, only one gene in the pair needs to be abnormal to cause symptoms of the condition. In families where asplenia appears to be inherited in an autosomal dominant manner, family members who carry the same non-working gene can have different symptoms and the severity of the condition may vary. In autosomal dominant inheritance, if an individual carries the non-working gene, he or she has a 50% chance of passing the gene on with each pregnancy.

In families where asplenia appears to be inherited in a X-linked manner, the gene causing the condition is located on the X chromosome. Since women have two X **chromosomes**, if a woman inherits the non-working gene on one of her X chromosomes, typically she will not have any symptoms of asplenia or will have a milder form of the condition. A woman who carries the X-linked form of asplenia will have a 50% chance of passing that non-working gene on with each pregnancy.

Since men tend to have one Y chromosome and one X chromosome, if it is a son that inherits the non-working gene, he will be affected with the condition. Men who have a X-linked form of asplenia will always pass their X chromosome containing the non-working gene on to all of their daughters, who would be carriers of the condition. In these families, asplenia will never be passed from the father to the son, since men give their sons a Y chromosome. If a woman who carries a X-linked condition passes the X chromosome containing the non-working gene to a daughter, then that daughter will be a carrier like her mother.

The pattern of inheritance of asplenia in a family is usually not obvious when there is only one individual diagnosed with the condition. Based on the families and studies performed on asplenia, the chance of a couple who have one child with asplenia having another child with the condition is approximately 5% or less. This chance may be higher if it is determined that asplenia is part of Heterotaxy syndrome, since there are a wider range of symptoms associated with that condition. Furthermore, if more than one family member has the diagnosis of asplenia, the chance of it occurring again in

KEY TERMS

Anomalous—Irregular or different from normal.

Anomalous venous return—Normally, the veins that bring blood containing oxygen from the lungs to the heart (called pulmonary veins) are connected to the left atrium. In this situation, the pulmonary veins are connected to the right atrium.

Asplenia—The absence of the spleen in the body.

Atria/Atrium—The upper chamber of the heart. Typically, there are two atrias, one on the right side and one on the left side of the heart.

Atrial septal defect—An opening between the right and left atria of the heart.

Congenital—Refers to a disorder which is present at birth.

Cyanosis—The bluish color of the skin that occurs when there is very low oxygen in the blood that is being transported throughout the body.

Echocardiography/Echocardiogram—An ultrasound examination targeted at the heart and performed by a cardiologist or an individual trained at detecting differences in the structure of the heart.

Isomerism—Refers to the organs that typically come in pairs, but where the right organ is structurally different from the left organ. In a condition like asplenia, the organs are identical.

Malrotation—An abnormality that occurs during the normal rotation of an organ or organ system.

Pulmonary atresia—When there is no valve between the right ventricle and the pulmonary artery (the artery leading from the heart to the lungs). In the absence of this valve, the blood does not flow into the lungs well.

Pulmonary stenosis—Narrowing of the pulmonary valve of the heart, between the right ventricle and the pulmonary artery, limiting the amount of blood going to the lungs.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

Transposition of the great arteries—A reversal of the two great arteries of the heart, causing blood containing oxygen to be carried back to the lungs and blood that is lacking in oxygen to be transported throughout the body.

Truncus arteriosus—Having only one artery coming from the heart instead of two. Often there is a ventricular septal defect (VSD) present.

Ventricular septal defect (VSD)—An opening between the right and left ventricles of the heart.

the family is based on the pattern of inheritance that the condition appears to be following.

Since asplenia appears to be inherited in different ways, it is theorized that there may be several different genes that could cause asplenia. This means that some families may have asplenia caused by one specific non-working gene, but in other families, a different non-working gene could cause the same condition to occur. As of 2001, the exact genes involved in causing asplenia have not been identified. However, there is ongoing research to identify the genes involved with this condition.

Demographics

It is estimated that the incidence of asplenia is low, approximately one in 10,000 to one in 20,000 live births. More males are affected with the condition than females. Asplenia also accounts for 1-3% of all **congenital heart defects**. Asplenia does not appear to occur more frequently in certain ethnic groups.

Signs and symptoms

Almost all individuals with asplenia have an abnormal or absent spleen. However, there are other organs and organ systems that can be affected.

Abdominal organs

SPLEEN As the name of the condition implies, the spleen is always affected in asplenia. The spleen in individuals with asplenia is either absent or does not develop completely (hypoplastic spleen). Since the spleen is involved in the body's immune system, these infants can have an abnormal immune system, which increases their risk for developing an infection.

DIGESTIVE TRACT DISORDERS There are several abnormalities that can occur with the digestive tract in individuals with asplenia. The most common digestive tract disorder associated with asplenia is malrotation of the intestine. Sometimes a digestive tract problem will present with symptoms of an obstruction in the digestive system, requiring emergency surgery.

STOMACH Most individuals with asplenia have their stomach located on the right side or in the center of the body instead of the left. In addition, individuals with asplenia can have a "twisted" stomach that could result in an obstruction in their digestive system and impair the blood supply to the stomach (gastric volvulus).

LIVER Normally, the liver is located on the right side of the body and the shape of the liver is not symmetrical. In asplenia, there can be isomerism of the liver—it can be located in the middle of the body, or located on the left side with the larger half of the liver located in the upper left side of the abdominal area.

GALLBLADDER The gallbladder may also be located in the middle of the body in individuals with asplenia.

Heart

Many infants with asplenia first present with cyanosis and severe respiratory distress. These are symptoms often seen in individuals who have a heart defect. Most individuals with asplenia have a defect in the structure and/or the position of their heart.

Typically, the heart is divided into two sides, a left and right, with each side containing two chambers, called ventricle and atrium. The left and right sides of the heart are different from each other in their structure and function. The job of the right side of the heart is to pump blood to the lungs to receive oxygen. The job of the left side of the heart is to receive the oxygenated blood from the lungs and pump it to the rest of the body. In asplenia, sometimes the structures of the right side of the heart are duplicated on the heart's left side.

A common heart defect often seen in asplenia is anomalous pulmonary venous return, which occurs when the pulmonary veins (the blood vessels that carry blood containing oxygen from the lungs to the heart) are connected to the right atrium instead of the left atrium. This causes the oxygenated blood to be pumped back to the lungs instead of the body. Sometimes, there is a hole between the right and left atrium (called atrial septal defect or ASD) that allows some of the oxygenated blood into the left atrium and pumped to the rest of the body.

Other heart defects frequently seen in individuals with asplenia include: common atrioventricular canal, common atrial canal, persistent truncus arteriosus, pulmonary stenosis or atresia, single ventricle in the heart, and transposition of the great arteries. Often there is more than one heart defect present. Furthermore, in many individuals with asplenia, the heart is located on the right side of the body instead of the left.

Lungs

Normally, the lungs are divided into lobes. The lung on the right side of the body usually has three lobes and the left lung typically has two lobes. In asplenia, each lung usually has three lobes.

There can be abnormalities in other systems of the body as well, but they are not often seen in most individuals with asplenia. Other abnormalities associated with asplenia include kidney anomalies, extra fingers and toes, **scoliosis**, facial abnormalities, and central nervous system anomalies.

Diagnosis

The diagnosis of asplenia is typically made by imaging studies. An echocardiogram of the heart can help identify any structural abnormalities and its exact position within the body. A chest x ray can also be used to locate the position of the heart and some of the other organs in the body. Ultrasound and CT examinations can also help determine if there are any malformations with the abdominal organs, the position of the stomach, the presence, appearance, and number of spleens, and how many lobes each lung has. While a MRI can also detect the presence and position of organs inside the body, it is less commonly used because of the need for sedation and the high cost of the test, especially in children.

Testing for the presence of Heinz and Howell-Jolly bodies in the blood has been suggested as a method to screen for an absent spleen. Howell-Jolly bodies are unique cells that tend to be present in the blood of individuals who do not have a spleen, but they can also be seen in the blood of individuals who have certain types of anemia. Therefore, this test should not be used as the sole diagnostic test for an absent spleen.

Some of the abnormalities seen in asplenia can be detected prenatally. Often the position of the heart and some of the heart defects can be diagnosed by fetal echocardiogram (an ultrasound examination of the fetal heart) in the late second and third trimesters of pregnancy. A fetal echocardiogram should be performed during pregnancy when a couple already has a child with asplenia. Additionally, a level II ultrasound examination can detect some digestive system anomalies, such as the position of the stomach.

Treatment and management

Surgery can sometimes be performed on the heart to repair the defect or defects. There are limitations to heart surgery and it cannot always be performed. Additionally,

heart surgery is not always successful. Surgery can also be used to correct many of the digestive tract disorders.

Additionally, because the spleen is involved in the body's immune system, it is recommended that all patients with the diagnosis of asplenia be given antibiotics and pneumococcal vaccination.

Prognosis

Without treatment, the prognosis of an infant diagnosed with asplenia is poor, with approximately 80% of these infants dying within the first year of life. The cause of death is usually complications from the heart defect. However, with advances in heart surgery and improvements in correcting many of the digestive tract anomalies, infants with asplenia are living much longer.

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Sharon A. Aufox, MS, CGC

Asplenia/polysplenia complex *see* **Asplenia**

Asthma

Definition

Asthma is a disease of the respiratory system that causes breathing difficulty. Asthma is typically expressed by repeated but reversible episodes of constriction and inflammation of the airways and lungs. Typical symptoms include wheezing, coughing, and shortness of breath. Technically, asthma is described as a chronic inflammatory disorder of the respiratory system. Asthma has both a genetic and environmental basis. The symptoms of asthma are caused by allergic-like reactions of the body's immune system to environmental and behavioral stimuli.

Description

Asthma is a chronic, life-long disease that affects the complex network of air passageways of the human respiratory system—the bronchial tubes (airways) and the lungs. Its symptoms range from mild discomfort to life threatening attacks that require immediate emergency treatment. Asthmatic patients can experience "asthma attacks" of varying degrees of severity. These episodes reduce the amount of air that can get in and out of the lungs. Severe asthma attacks can leave individuals gasping for air.

An asthma attack involves the constriction (narrowing) and swelling (inflammation) of the airways (bronchi and bronchioles) and inflammation of the lining of the lungs. As the lining of the airways become inflamed, more mucus is produced. The extra fluid in the mucus is the body's way of removing foreign substances, such as allergens, that come into contact with body tissues. In medical terms, the narrowing or constriction of the airways is referred to as an "obstruction." Persistent or chronic inflammation of the airways can cause permanent damage and reduce lung function so that breathing becomes less efficient.

Typical symptoms of asthma include wheezing, coughing, shortness of breath, and tightening of the chest. It is a life-long, chronic condition. Currently, there is no "cure" for asthma, but new, more effective medications and careful management of the disease can help asthmatic patients maintain a quality, active lifestyle.

Chronic asthma is the result of an interaction between heredity and environment. Research has confirmed that some people inherit a strong genetic disposition for asthma that can be "triggered" by a variety of possible environmental factors, such as repeated exposure to irritants such as dust mites, pet hairs, and tobacco smoke.

Modern medical treatment focuses on helping asthma patients achieve control over their own asthma situation on a day to day basis. Another important goal is

reducing the incidence of severe attacks in patients with the most serious or advanced stages of this disease.

One of the most troubling aspects about asthma is that, despite recent advances in basic research and clinical treatment, scientists have not yet unraveled the complex physiological mechanisms and processes that cause the disease condition referred to as asthma. Also, it is often not possible to pinpoint the exact nature of the triggers that initiate asthmatic symptoms in specific individuals.

There is still no "cure" for asthma, but ongoing medical research has led to improved treatment and management that has dramatically improved the quality of life for people who have asthma. An improvement in environmental conditions in which asthmatics live can reduce the number and severity of asthma attacks and may actually decrease the number of people sensitized to environmental triggers.

In the long term, scientists hope to discover ways to prevent the development of asthma in individuals who have a genetic predisposition for this disease. The medical term for this approach is "primary prevention intervention."

Unfortunately, the number of asthma cases around the world is increasing at an alarming rate—so fast, in fact, that leading medical authorities now refer to this disease as the "asthma epidemic." At the beginning of the new millennium, more people in the United States die of chronic diseases, such as asthma, than the ancient scourge of infectious diseases, such as tuberculosis and influenza.

In normal breathing, air enters the nose or mouth, travels down the trachea (windpipe) in the throat and then is carried through a branching network of tubes—the bronchi—to each part of the lungs. These airways end in the alveoli (tiny air sacs) that make up the sponge-like tissues of the lungs. Oxygen and carbon dioxide are exchanged with the blood circulating within the blood vessels surrounding the air sacs. Under the microscope, these air spaces give the human lung tissue a somewhat sponge-like appearance. Asthma attacks not only the bronchial tubes leading to the lungs, but also the entire network of air passageways within the lungs, including the alveoli. Over time, repeated asthmatic episodes cause permanent changes that decrease the size of the airways. The medical term for this change is the "remodeling" of the airways.

Genetic profile

Current medical research continues to refine our understanding of how genes influence the development and severity of asthma symptoms in individual patients. It has been clearly established that asthma tends to run in families. Recent research, including studies that trace the appearance of asthma in families with twins, suggests that one's genetic makeup rather than environment is the major factor in determining an individual's predisposition—or potential—for developing asthma. Studies show that identical twins are more likely to share a genetic predisposition for asthma than are fraternal (non-identical) twins. Still, it is the presence of allergens and other substances in the environment that actually stimulate or "turn on" the genes that are related to asthma.

Determining the role of **inheritance** in asthma is made more difficult because many different genes seem to be involved in controlling the development and expression of asthma. Thus, there is no clear Mendelian pattern of inheritance of asthma such as in **sickle cell anemia** disease, which is clearly controlled by the presence or absence of a single **gene** for that disease.

Some scientists suspect that as many as 20 or more different genes may control an individual's potential for developing asthma. Scientists refer to this multi-gene component as *polygenic heritability*. Children of asthmatic parents have about a 30% chance of developing chronic asthma.

The task of identifying the specific genes responsible for various asthma symptoms will be made easier by the **Human Genome Project**. This mammoth research project has identified all of the genes that make up the 23 pairs of **chromosomes** in human cells. Much work remains in learning the role of each of these genes in the human body.

Asthma and the immune system

Research studies show that specific symptoms experienced by asthma patients, such as the inflammation of the airways and lungs, are initiated by the action of genes that regulate the activity of the human immune system. In other words, these genes control how the immune system responds to the presence of substances that can potentially trigger asthma symptoms.

Like a modern army, the human immune system consists of a wide array of specialized devices that work together to "neutralize enemy forces." In human terms, the "enemy forces" are antigens, the term given to any foreign agent invading the body. Antigens include disease producing organisms and toxic chemicals in the environment. The human equivalent of "specialized devices" is a complex network of cells in the immune system. Some of these cells produce antibodies, large molecules made up of proteins, that attack specific types of antigens.

KEY TERMS

Allele—One of two or more alternate forms of a gene.

Allergen—A substance or organism foreign to the body. Allergens stimulate the immune system to produce antibodies.

Allergic rhinitis—Hay fever.

Allergy—Condition in which the immune system is hypersensitive to contact with allergens; an abnormal response by the immune system to contact with an allergen. This condition produces symptoms such as inflammation of tissues and production of excess mucus in respiratory system.

Antibody—A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

Antigen—A substance or organism that is foreign to the body and stimulates a response from the immune system.

Atopic—A condition or disease that is the result of an allergic reaction.

Atopic asthma—Asthma caused by an allergic reaction; atopic asthma tends to have a strong inherited component (tends to run in families).

Atopic rhinitis—Also referred to as "hay fever"; symptoms of rhinitis caused by an allergic response to the presence of an allergen (such as tree or grass pollen).

Bronchi—Branching tube-like structures that carry air in and out of the lungs; walls of bronchi contain circular muscles that can constrict (tighten up to make airways narrower) or dilate (relax to make airways wider); bronchi divide into smaller bronchioles within the lung tissue.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genetic disease—A disease that is (partly or completely) the result of the abnormal function or expression of a gene; a disease caused by the inheritance and expression of a genetic mutation.

Histamine—A substance released by immune system cells in response to the presence of an allergen; stimulates widening of blood vessels and increased porousness of blood vessel walls so that fluid and protein leaks out from blood to surrounding tissue, causing inflammation of local tissues.

Hypersensitive—A process or reaction that occurs at above normal levels; overreaction to a stimulus.

IgE—An antibody composed of protein; specific forms of IgE produced by cells of immune system in response to different antigens that contact the body; major factor that stimulates the allergic response.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Inflammation—Swelling and reddening of tissue; usually caused by the immune system's response to the body's contact with an allergen.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Recessive gene—A type of gene that is not expressed as a trait unless inherited by both parents.

Rhinitis—Infection of the nasal passages.

Sensitization—Change in immune system so that it identifies and "remembers" specific properties of an antigen.

The immune system "remembers" its contact with specific antigens, such as viruses, bacteria, and other pathogenic organisms, house dust mites, and plant pollen. Any subsequent—or future—encounter with a "known" antigen stimulates the immune system to produce antibodies that specifically target that antigen.

IgE antibodies

In more detail, scientists have identified a specific set of genes (on the long arm of Chromosome 5, to be exact) that force the immune system to make above normal amounts of the allergic antibody called Immunoglobulin E (IgE) in asthmatic patients. IgE is an

antibody composed of a large Y-shaped protein molecule. The immune system produces this antibody in response to the presence of foreign substances—allergens—such as dust mites or pet hair. IgE is made by the plasma cells of the immune system. It is the key culprit in the process that creates the symptoms of asthma. IgE plays a critical role in initiating the inflammation of the respiratory tract, which is a primary cause of asthma attacks. A research study suggests that asthmatic patients produce higher levels of IgE antibodies in response to allergens such as house dust mites than do people without asthma.

A possible explanation for this overproduction of IgE antibodies could be related to a lack of exposure to common childhood illnesses. For example, cold viruses and other respiratory illnesses stimulate the human immune system to produce a certain type of helper T cell that specifically targets these disease agents. However, in the absence of such stimuli, the immune system instead produces another type of helper T cell that initiates the production of the IgE antibody.

IgE antibodies coat the surfaces of mast cells and white blood cells, called basophils, which are part of the immune system. The base of the Y of the IgE molecules attach to basophils in the blood and to mast cells, which are found in the connective tissue of the lungs, skin, tongue, and lining of the nose. Mast cells are sentries that rapidly react to the presence of antigens that trigger acute asthmatic incidents.

Some of the foreign antigens entering the respiratory airways will become attached to the extended arms of IgE molecules on the surface of the mast cells. This combination of antigen and antibody triggers these cells to release histamines and other substances into nearby tissues. Histamines are a type of chemical signal that initiates the inflammatory response, one of the primary symptoms of asthma. Inflammation involves increased blood flow to affected tissues. Histamines stimulate the dilation—widening—of the walls of blood vessels and make them more porous so that more blood fluid and proteins leak out of the blood vessels and into surrounding tissue, causing the swelling and reddening typical of inflammation. This inflammation, along with the constriction of the muscles in walls of the bronchial airways, narrows the air passages and makes breathing more difficult. These changes are what is referred to as an asthma attack.

Other studies have also suggested that the genes that are responsible for making the bronchial passageways "over reactive" (increasing the tendency of constricting or narrowing) in asthmatic patients are quite distinct from the genes that regulate the action of the immune system.

Recent genetic research may result in some major changes in our understanding of the role of specific genes in asthma. British scientists have tentatively identified a single gene that could be responsible for as many as 40–50% of all asthma cases. The U.K. scientists also suggest that four other genes may also play a significant role in the development of asthma. It is generally believed that some genes may simply enhance—magnify or reinforce—the action of other genes that are primarily responsible for triggering asthma. This task of unraveling the genetics of asthma is made more complicated by the variety of ways in which these genes can interact in different people.

Demographics

United States statistics

Asthma is the most prevalent childhood chronic disease. According to the Centers for Disease Control, approximately 17 million Americans exhibit symptoms of asthma—about five million of those are under the age of 18. More than 50% of asthma cases occur in children between two and 17 years of age. At a younger age, studies indicate that boys are twice as likely to develop asthma than girls. But this imbalance disappears in older age groups.

Asthma is the primary cause of school absenteeism. Asthma is also one of the most prevalent diseases in the workplace. Asthma accounts for approximately three million lost work days for adults and 10.1 million lost school days for children each year in the United States.

According to a recent American Lung Association report, double the number of adult female patients require emergency medical care for their asthma than do adult male patients. It is thought that the differences in male and female hormones may cause this disparity.

In the United States, the mortality rate—number of deaths—attributed to asthma increased 56% from 1979 to 1998. Asthma kills more than 5,000 Americans each year. Doctors believe that most of these fatalities could have been prevented with proper care and treatment.

In general, it is difficult to pinpoint the precise causes of the dramatic increase in asthma cases in the United States. One important factor may be partly due to poor diagnosis and management of individual cases of asthma, especially in less privileged or minority populations. However, after many years of rapid increases in asthma cases, some of the most recent evidence suggests that the number of asthma cases may actually be declining slightly. Further studies will be needed to confirm this trend.

International statistics

Asthma has been described as the fastest growing chronic disease and a world-wide epidemic. Approximately 25,000 children die of asthma each year throughout the world. According to Global Initiative for Asthma (GINA), a world-wide asthma research and education program, there are over 150 million asthmatic individuals worldwide. In most countries, asthmatic cases are increasing 20–50% every decade. Every ten years, asthma claims over one million lives. Some studies have revealed a 75% increase in asthma cases between 1980 and 1994 globally. Children accounted for the greatest increase in numbers.

It is interesting to note that the incidence of asthma varies greatly throughout the world. While about 2% of children in China display symptoms of asthma, approximately 30% of young people in Britain have indications of this disease. In Australia, the incidence of asthma is very high in Caucasian children, but much lower in Aboriginal children.

Why such variations exist in the prevalence of asthma in different populations remains an unsolved mystery. Some scientists speculate that lifestyle factors, such as a lack of physical activity, increased obesity, and more time spent indoors may contribute to higher rates of asthma in more highly developed countries. It is also possible that environmental irritants such as poor indoor and outdoor air quality, along with the presence of potent irritants such as cockroach allergens, may contribute to higher rates of childhood asthma in poorer communities. Other factors that may prompt the onset of asthma are viral respiratory infections, low birth weight, and smaller than average air passageways in asthmatic patients.

Another area of research concerns the connection between common childhood infections and asthma. Many studies have shown that children who are exposed to viruses that cause the common cold and other respiratory infections at a very young age are less likely to develop asthma than their peers living in a more "hygienic" environment. So children living at home with older siblings and those who spend part of their week in daycare centers may be less likely to develop asthma than children who do not interact with others of their own age group.

A related factor could be the overuse of antibiotics. The frequent use of antibiotic medications to treat relatively minor infections may produce changes in a patient's immune system that may increase his or her chance of developing asthma at some point later in life.

A young girl is using an inhaler to facilitate breathing. *(Custom Medical Stock Photo, Inc.)*

Other studies have documented higher rates of childhood asthma in some less advantaged, minority inner city populations in the United States than in wealthier suburban communities. In these populations, exposure to cockroach allergens may be the major culprit.

Personalities with asthma

The symptoms of asthma have been observed and recorded in the medical literature since the time of Hippocrates, a famous doctor living in ancient Grecian times. The National Library of Medicine-Breath of Life Exhibit identifies many well known personalities who had a medical history of asthma. Despite their illness, they pursued their chosen professions with great vigor and energy. The prolific American musician, Leonard Bernstein, who composed *West Side Story* as well as many other celebrated scores, struggled with asthma throughout his life. Another classical composer from a much earlier era, Ludwig von Beethoven, wrote some of history's most memorable music while coping with chronic asthma and without the benefit of modern medical treatment. Robert Joffrey, founder of the avant-garde Joffrey Ballet, pursued an active dancing career in spite of his asthma. Contemporary individuals with asthma include the folk singer Judy Collins, track and field champion Jackie Joyner-Kersee, and professional basketball star Dennis Rodman.

John Kennedy, 35th president of the United States, developed asthma from allergies to dogs, horses, and other animals. Some of his predecessors, including Theodore Roosevelt, Woodrow Wilson, and Calvin Coolidge, also had asthma.

Signs and symptoms

The symptoms experienced by patients with asthma are caused by "hyper responsiveness"—an overly sensi-

tive response—of the body's immune system to environmental or behavioral factors, such as allergies and exercise. Asthma patients are encouraged to learn to recognize their own special pattern of early warning signs that signal the start of an asthma episode. Asthma symptoms can be quite variable and are usually reversible. It is possible to classify individual cases of asthma as mild, moderate, or severe. Classification is based on the severity and frequency at which symptoms are experienced. The typical characteristics of each category are:

Mild persistent asthma

Children who experience symptoms of wheezing, coughing, or breathing difficulty less than once a day but more than twice a week.

Moderate asthma

Patients who experience asthma symptoms each day and require daily medication. Symptoms may persist for many days and may interfere with normal physical activity.

Severe asthma

Patients with severe asthma have ongoing, persistent symptoms of this disease. Severe attacks are rare, but much more serious, and can be life threatening.

Asthma episodes can vary from mild to severe attacks. The first signs of a mild or moderate attack could be a slight tightening of the chest, coughing, and spitting up of mucus. The patient may start wheezing as a result of trying to inhale and exhale through constricted air passageways.

Severe attacks can bring on a feeling of extreme tightening of the neck and chest, making breathing increasingly difficult. Patients may struggle to speak or breathe. In advanced stages of severe attacks, lips and fingernails may take on a grayish or bluish tinge indicating declining oxygen levels in the blood. Such attacks can be fatal in the absence of prompt medical attention.

Diagnosis

Medical diagnosis for asthma involves a complete physical checkup. One of the most important tests is the measurement of pulmonary (lung) function—the volume of air a patient can inhale (breathe in) and exhale (breathe out). Peak flow meters and spirometers are devices that are used to measure breathing efficiency and lung capacity.

The patient's history can also provide critical clues that can confirm a diagnosis of asthma and can help to identify the factors that contributed to the development of the disease. Doctors need to know about any patterns in the occurrence of symptoms (such as seasonal variations), when asthma symptoms first appeared, any connection between symptoms and exposure to possible allergens, any disturbances in sleep patterns, and the nature of previous illnesses. Other diagnostic tests may include x rays to eliminate other possible causes of airway obstruction (blockage) and allergy tests. Various blood tests may also be performed.

Early clues that indicate a patient may have asthma include difficulty in breathing, restlessness or persistent coughing while sleeping, general feeling of tiredness and lack of energy, a persistent stuffy nose, and frequent sneezing. Other signs are coughing or wheezing during or after physical activity and frequent colds that often involve chest congestion. Asthmatic patients are also more likely to develop other respiratory diseases such as pneumonia.

Asthma triggers

Asthmatic patients are surrounded by an environmental minefield. Many indoor and outdoor factors can trigger or initiate typical symptoms of asthma, including allergies, viral respiratory infections, weather changes, and exercise. Medications containing aspirin also act as an asthma trigger in about 10–20% of adult asthmatic patients. Allergens, such as inhaled dust particles and plant pollen, are substances that can stimulate an allergic response.

Asthma and allergies

Many studies have confirmed that allergies cause the greatest majority of childhood asthma cases. Doctors refer to cases of asthma that are caused by allergies as atopic asthma. Atopic asthma is the most common form of asthma and tends to run in families. It is an inherited over reaction—hypersensitivity—to allergens in the environment and the related overproduction of IgE antibodies by the human immune system. Antibodies produced by the immune system combine with allergens. This action stimulates an asthma attack, in which the immune system releases substances that bring on the constriction and inflammation of the airways of the lungs.

More than 80% of asthmatic patients also suffer from allergies such as hay fever. The medical term for hay fever is allergic rhinitis. Allergic rhinitis is the most common cause of atopic asthma. Many types of allergens can trigger the immune system to produce the typical hay fever symptoms that mainly affect the nasal region, such as stuffiness and a runny nose. The term "hay fever" does not accurately describe this problem, because it is rarely

caused by hay and does not produce a fever in affected patients. Allergies even aggravate asthma in patients whose asthma was not originally caused by allergic factors. Small amounts of inhaled or swallowed allergens do not directly harm the tissues of the airways and lungs. However, they unfortunately act as triggers that set off the chain of events in the immune system that produce the symptoms typical of asthma.

People with asthma have increased sensitivity to allergens in the air they breathe in. Allergies are the human immune system's reaction to biological triggers—including indoor allergens such as dust mites, animal dander (pet hair or feathers), saliva, flakes of skin, secretions from pets and insects, mold, and substances found in food. Even "hairless" dogs can be a problem for asthmatic patients. Some foods, such as peanut, dairy products, and seafood, can cause attacks in some asthmatic children. Food additives, such as sulfites, and even natural foods like eggs, shellfish, and raw vegetables can act as triggers for asthma. Endotoxins, which are chemicals produced by molds growing on farm products, may contribute to asthma in agricultural areas. Synthetic (man-made) products like the latex material used in surgical gloves can also trigger asthma episodes.

In some of the more "developed" countries, an important contributing factor in the growing number of atopic asthma cases may be the reduced exposure to common childhood respiratory infections such as the flu and colds. Recent studies have shown that children who live in very clean, hygienic conditions and are relatively isolated from other young people are more likely to develop asthma later in life. This is commonly referred to as the "hygiene theory." It seems that children with older siblings and who attend day care programs where they may contract such illnesses have a lower risk for developing asthma. A possible explanation for this seemingly strange connection is that a child's immune system is fine tuned, or conditioned, by contact with these infectious organisms and other foreign agents at a very young age.

Non-allergic factors

Non-allergic factors that can stimulate or aggravate asthma symptoms include tobacco smoke, chalk dust and talcum powder, cooking fumes, and fumes from chemicals such as household cleaners. Certain behaviors such as stress and emotional anxiety can also trigger asthmatic attacks. Young children can develop asthma or cause asthmatic episodes as a result of viral infections such as colds, flu, and pneumonia.

Exercise is a common trigger for asthma in about 80% of asthmatic individuals. In some asthmatic patients, exercise induces typical asthma symptoms such as coughing, wheezing, and shortness of breath. Symptoms may appear during or after participation in physical activity. Pretreatment medications, such as short-acting bronchiodilators, quickly widen the air passages and thus help prevent the onset of asthma while a patient participates in physical activities. Some doctors advise their asthmatic patients to participate in sports like baseball or football that provide frequent breaks in activity rather than prolonged endurance sports such as swimming and long distance running.

Asthma does not have to be a barrier to participating in athletic activities. For example, 67 of the 596 members of the United States team at the 1984 Olympics tested positive for exercise-induced asthma, and that team won 41 Olympic medals. In addition, another survey revealed that 50% of the athletes participating in the 1996 Olympics displayed some form of asthmatic symptoms.

Changes in the weather, such as temperature and humidity variations can also negatively affect asthma patients. Winter is a tough time for people with asthma. They have difficulty in conditioning—warming up and humidifying—the air they breathe in. Some people with asthma wear a surgical mask that can trap warm, moist air that is exhaled with each breath. During cold weather, these individuals tend to spend more time indoors where they are more likely to catch contagious viral infections. Viral infections of the respiratory system are more likely to trigger severe asthmatic attacks during the winter months. In addition, unclean and poorly maintained forced air heating systems release many pollutants that further aggravate asthmatic symptoms.

Some remedies that could improve the quality of life for patients with asthma may also benefit the entire community in which they live. One study provides more evidence for a link between air pollution and asthma. During the 1996 Olympics, there were 42% fewer emergency hospital visits for treatment of severe asthma attacks in the Atlanta area. It is thought that this decline was linked to a sharp, but temporary, reduction in auto pollution caused by more people taking public transit instead of driving their cars during the two week event. So, cutting down on traffic congestion may help asthma patients breathe easier.

Every asthma patient is unique. Because there are so many environmental conditions that can affect people with the genetic predisposition for asthma, it is often difficult to pinpoint the primary cause of the disease in individual cases.

Treatment and management

Like all chronic diseases, asthma requires specialized medical care and attention. Doctors and other health

professionals work in partnership with asthma patients to develop comprehensive, individualized management plans that help them cope with their asthma on a day to day basis. An effective management plan can reduce the incidence of serious asthma attacks and the need for emergency medical care. The key features of an asthma management plan include:

- learning about early warning signs and symptoms of asthma
- regular monitoring and recording of the appearance of asthma-related symptoms
- monitoring lung function
- learning how to use prescribed medications
- avoiding activities, such as prolonged exercise, that can trigger an asthma attack
- avoiding contact with possible environmental triggers, such as pets, allergens, tobacco smoke, etc.
- maintaining healthy lifestyle by controlling weight gain, salt intake, blood pressure, and blood cholesterol levels

Specific goals of asthma management programs include:

- controlling and minimizing chronic symptoms such as coughing and breathlessness early in the morning, at night, and after exercise
- achieving healthy pulmonary (lung) function as much as possible
- requiring the smallest possible dosage of medicine required to effectively control asthma symptoms, so that side effects from medications can be minimized

With the newer, more effective medications now available, it is possible to provide patients with good short term and long term control of asthmatic symptoms. Asthma patients use both rescue medications and controllers, which provide long-term control of asthma symptoms. Most asthma patients take their asthma medicine with the aid of metered-dose inhalers. These handheld devices deliver precise dosages of medication in the form of a pressurized spray that is inhaled orally by the user. Another device that delivers medication in spray-form are "nebulizers," which are sometimes used by younger children and hospitalized patients who are unable to properly manipulate inhalers.

Rescue medications include bronchodilators, which provide short term, rapid relief from the symptoms of an asthma attack after it has started. These medications act by relaxing the circular muscles in the bronchial tubes that connect to the lungs. As the muscles relax, the air ways become wider, making breathing easier. Bronchodilators alleviate or reduce the feeling of tightness in lungs due to inflammation.

Controllers such as corticosteroids are anti-inflammatory medications that help prevent asthma attacks from happening. They help to prevent or reduce the onset of typical asthma symptoms that interfere with normal breathing, such as the build-up of mucus and the inflammation of the tissues that line the airways and lungs. Most anti-inflammatory drugs work by suppressing or interfering with the action of histamines after they have been released by cells of the immune system. Corticosteroids are often taken twice daily. They provide prolonged relief and help reduce long-term damage to the lungs.

Bronchodilators and corticosteroids are the principle medications for the treatment and management of persistent asthma symptoms. Patients can also monitor the function of the their respiratory system with the aid of peak flow meters and spirometers. These devices measure the amount of air exhaled with each breath. They are used to regularly monitor the severity of asthma symptoms and to evaluate and manage treatment procedures for individual patients.

Emergency treatment

Emergency care in a hospital setting includes treating patients with bronchodilators and corticosteroids. Asthma attacks reach the life-threatening stage when the patient's airway continues to constrict—referred to as airflow obstruction—and breathing becomes weaker and weaker. In critical cases, additional medications and oxygen may be administered in an attempt to restore normal respiratory activity. Delayed access to emergency treatment can lead to complete respiratory failure—the patient simply stops breathing and cannot be revived.

Under diagnosis

Unfortunately, many asthmatic children receive inadequate treatment and access to asthma medications. One survey reported that less than 40% of children had regular access to controller medications. In this group there was a clear over-dependence on rescue medications. This under-treated population required more frequent emergency hospital visits than those patients who were on a well-managed program. Under diagnosis and poor treatment are also major causes of mortality, or death, due to asthma.

Health providers advise coaches and other sporting officials to be more aware of emergency treatments, such as dealing with asthmatic attacks, that may be required for asthmatic students participating in sporting activities.

Allergy shots

Allergy shots, also known as allergen immunotherapy, are recommended for people who suffer from atopic asthma when their daily routine makes it difficult for them to avoid contact with suspect allergens, such as dust mites, pet dander, and grass pollen. A series of shots with gradually increasing amounts of allergen may be given over a number of months or even years. The shots are actually vaccines containing various allergens, such as pollen or dust mites. This increased exposure to the allergen seems to desensitize the body's immune system to these allergy triggers. Allergy shots can diminish the severity of asthma symptoms and also lower the dosages of other asthma medications that patients must take to keep their asthma under control.

In more detail, research studies suggest that allergy shots work by modifying the behavior of the important Th1 and Th2 cells of the immune system. Immunotherapy might activate Th1 cells (which produce "normal" immune responses) and depress the activity of Th2 cells, which release substances that stimulate plasma cells to make the IgE antibody.

Medical research and experimental treatments

A new experimental procedure involves injecting "anti-IgE" substances that combine with IgE in the blood. This prevents IgE from stimulating the release of histamine from mast cells. It is hoped that anti-IgE treatments would reduce the amount of corticosteroid use by asthmatic patients. So far, this form of treatment provides only temporary relief and scientists are actively searching for more effective anti-IgE medications.

Future research may lead to the development of genetic screening tests that can identify children who may be at risk for developing asthma. Such at-risk children could then be placed in early intervention programs that would be designed to help them avoid specific situations that could set off their immune systems and produce typical asthma symptoms.

A number of major **gene therapy** research projects are now focusing on developing new techniques for controlling the activity of genes involved in producing symptoms of asthma. Researchers want to figure out how to shut off or reduce the intensity of typical symptoms of asthma without impairing normal body function.

Currently, no cure exists for asthma. However, medical research is continuing its quest to gain a better understanding of the physiological and genetic basis of asthma. New medications are providing more effective long term and short term control of asthma symptoms.

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Marshall G. Letcher, MA

Ataxia-telangiectasia

Definition

Ataxia-telangiectasia (A-T) is a rare, genetic neurological disorder that progressively affects various systems in the body. Children affected with A-T appear normal at birth; however, the first signs of the disease—usually a lack of balance and slurred speech—often appear between one and two years of age.

Description

The onset of cerebellar ataxia (unsteadiness and lack of coordination) marks the beginning of progressive degeneration of the cerebellum, the part of the brain responsible for motor control (movement). This degeneration gradually leads to a general lack of muscle control, and eventually confines the patient to a wheelchair. Children with A-T become unable to feed or dress themselves without assistance. Because of the worsening ataxia, children with A-T lose their ability to write, and speech also becomes slowed and slurred. Even reading eventually becomes impossible, as eye movements become difficult to control.

Soon after the onset of the ataxia, an individual usually exhibits another symptom of the disease: telangiectases, or tiny red spider veins (dilated blood vessels). These telangiectases appear in the corners of the eyes—giving the eyes a blood-shot appearance—or on the surfaces of the ears and cheeks exposed to sunlight.

In about 70% of children with A-T, another symptom of the disease is present: an immune system deficiency that usually leads to recurrent respiratory infections. In many patients, these infections can become life threatening. Due to deficient levels of IgA and IgE immunoglobulins—the natural infection-fighting agents in the

blood—children with A-T are highly susceptible to lung infections that are resistant to the standard antibiotic treatment. For these patients, the combination of a weakened immune system and progressive ataxia can ultimately lead to pneumonia as a cause of death.

Children with A-T tend to develop malignancies of the blood circulatory system almost 1,000 times more frequently than the general population. Lymphomas (malignant tumors of lymphoid tissues) and leukemias (abnormal overgrowth of white blood cells, causing tumor cells to grow) are particularly common types of **cancer**, although the risk of developing most types of cancer is high in those with A-T. Another characteristic of the disease is an increased sensitivity to ionizing radiation (high-energy radiation such as x rays), which means that patients with A-T frequently cannot tolerate the radiation treatments often given to cancer patients.

Genetic profile

Ataxia-telangiectasia is called a recessive genetic disorder because parents do not exhibit symptoms; however, each parent carries a recessive (unexpressed) **gene** that may cause A-T in offspring. The genetic path of A-T is therefore impossible to predict. The recessive gene may lie dormant for generations until two people with the defective gene have children. When two such A-T carriers have a child together, there is a 1-in-4 chance (25% risk) of having a child with A-T. Every healthy sibling of a child with A-T has a 2-in-3 chance (66% risk) of being a carrier, like his or her parents.

The A-T gene (called ATM, or A-T Mutated) was discovered by Tel Aviv researchers in 1995. The ATM protein is thought to prevent damaged **DNA** from being reproduced. However, the cells of patients with A-T lack the ATM protein, although the cells of those with the mild form of the disorder contain small amounts of it. It is thought that ATM is involved in sending messages to several other regulating proteins in the body. The absence of ATM severely disrupts the transmission of these messages, thereby affecting many different systems of the body.

Scientists have found that the ATM gene is often found with the p53 gene, which is defective in the majority of cancerous tumors. Tumor biologists, therefore, view A-T as one of the most explicit human models for studying inherited cancer susceptibility. In children who have A-T, the defective A-T gene blocks the normal development of the thymus, the organ most important for the development of the immune response. Understanding how immunodeficiencies develop in children with A-T may have relevance to research on other immunodeficiency disorders.

Demographics

Both males and females are equally affected by A-T. Epidemiologists estimate the frequency of A-T as between 1/40,000 and 1/100,000 live births. However, it is believed that many children with A-T, particularly those who die at a young age, are never properly diagnosed. Thus, the disease may occur much more often than reported.

It is also estimated that about 1% (2.5 million) of the American population carry a copy of the defective A-T gene. According to some researchers, these gene carriers may also have an increased sensitivity to ionizing radiation and have a significantly higher risk of developing cancer—particularly **breast cancer** in female carriers.

Signs and symptoms

Although there is much variability in A-T symptoms among patients, the signs of A-T almost always include the appearance of ataxia between the ages of two and

KEY TERMS

Alpha-fetoprotein (AFP)—A chemical substance produced by the fetus and found in the fetal circulation. AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

Atrophy—Wasting away of normal tissue or an organ due to degeneration of the cells.

Cerebellar ataxia—Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

Dysarthria—Slurred speech.

Dysplasia—The abnormal growth or development of a tissue or organ.

Immunoglobulin—A protein molecule formed by mature B cells in response to foreign proteins in the body; the building blocks for antibodies.

Ionizing radiation—High-energy radiation such as that produced by x rays.

Leukemia—Cancer of the blood forming organs which results in an overproduction of white blood cells.

Lymphoma—A malignant tumor of the lymph nodes.

Recessive gene—A type of gene that is not expressed as a trait unless inherited by both parents.

Telangiectasis—Very small arteriovenous malformations, or connections between the arteries and veins. The result is small red spots on the skin known as “spider veins”.

five. Other, less consistent symptoms may include neurological, cutaneous (skin), and a variety of other conditions.

Neurological

Neurological symptoms of A-T include:

- Progressive cerebellar ataxia (although ataxia may appear static between the ages of two and five)
- Cerebellar dysarthria (slurred speech)
- Difficulty swallowing, causing choking and drooling
- Progressive apraxia (lack of control) of eye movements
- Muscle weakness and poor reflexes
- Initially normal intelligence, sometimes with later regression to mildly retarded range

Cutaneous

Cutaneous symptoms include:

- Progressive telangiectases of the eye and skin develop between two to ten years of age
- Atopic dermatitis (itchy skin)
- Café au lait spots (pale brown areas of skin)
- Cutaneous atrophy (wasting away)
- Hypo- and hyperpigmentation (underpigmented and overpigmented areas of skin)
- Loss of skin elasticity
- Nummular eczema (coin-shaped inflammatory skin condition)

Other symptoms

Other manifestations of A-T include:

- Susceptibility to neoplasms (tumors or growths)
- Endocrine abnormalities
- Tendency to develop insulin-resistant diabetes in adolescence
- Recurrent sinopulmonary infection (involving the sinuses and the airways of the lungs)
- Characteristic loss of facial muscle tone
- Absence or **dysplasia** (abnormal development of tissue) of thymus gland
- Jerky, involuntary movements
- Slowed growth
- Prematurely graying hair

Diagnosis

For a doctor who is familiar with A-T, the diagnosis can usually be made on purely clinical grounds and often on inspection. But because most physicians have never seen a case of A-T, misdiagnoses are likely to occur. For example, physicians examining ataxic children frequently rule out A-T if telangiectases are not observed. However, telangiectases often do not appear until the age of six, and sometimes appear at a much older age. In addition, a history of recurrent sinopulmonary infections might increase suspicion of A-T, but about 30% of patients with A-T exhibit no immune system deficiencies.

The most common early misdiagnosis is that of static encephalopathy—a brain dysfunction, or ataxic cerebral palsy—paralysis due to a birth defect. Ataxia involving the trunk and gait is almost always the presenting symptom of A-T. And although this ataxia is slowly and steadily progressive, it may be compensated for—and masked—by the normal development of motor skills between the ages of two and five. Thus, until the progression of the disease becomes apparent, clinical diagnosis may be imprecise or inaccurate unless the patient has an affected sibling.

Once disease progression becomes apparent, **Friedreich ataxia** (a degenerative disease of the spinal cord) becomes the most common misdiagnosis. However, Friedreich ataxia usually has a later onset. In addition, the spinal signs involving posterior and lateral columns along the positive Romberg's sign (inability to maintain balance when the eyes are shut and feet are close together) distinguish this type of spinal ataxia from the cerebellar ataxia of A-T.

Distinguishing A-T from other disorders (differential diagnosis) is ultimately made on the basis of laboratory tests. The most consistent laboratory marker of A-T is an elevated level of serum alpha-fetoprotein (a protein that stimulates the production of antibodies) after the age of two years. Prenatal diagnosis is possible through the measurement of alpha-fetoprotein levels in amniotic fluid and the documentation of increased spontaneous chromosomal breakage of amniotic cell DNA. Diagnostic support may also be offered by a finding of low serum IgA, IgG and/or IgE. However, these immune system findings vary from patient to patient and are not abnormal in all individuals.

The presence of spontaneous chromosome breaks and rearrangements in lymphocytes in vitro (test tube) and in cultured skin fibroblasts (cells from which connective tissue is made) is also an important laboratory marker of A-T. And finally, reduced survival of lymphocyte (cells present in the blood and lymphatic tissues) and fibroblast cultures, after exposure to ionizing radiation, will confirm a diagnosis of A-T, although this technique is performed in specialized laboratories and is not routinely available to physicians.

When the mutated A-T gene (ATM) has been identified by researchers, it is possible to confirm a diagnosis by screening the patient's DNA for mutations. However,

in most cases the large size of the ATM gene and the large number of possible mutations in patients with A-T seriously limit the usefulness of mutation analysis as a diagnostic tool or method of carrier identification.

Treatment and management

There is no specific treatment for A-T because **gene therapy** has not become an option as of year 2000. Also, the disease is usually not diagnosed until the individual has developed health problems. Treatment is therefore focused on the observed conditions, especially if neoplams are present. However, radiation therapy must be minimized to avoid inducing further chromosomal damage and tumor growth.

Supportive therapy is available to reduce the symptoms of drooling, twitching, and ataxia, but individual responses to specific medications vary. The use of sunscreens to retard skin changes due to premature aging can be helpful. In addition, early use of pulmonary physiotherapy, physical therapy, and speech therapy is also important to minimize muscle contractures (shortening or tightening of muscles).

Although its use has not been formally tested, some researchers recommend the use of antioxidants (such as vitamin E) in patients with A-T. Antioxidants help to reduce oxidative damage to cells.

Prognosis

A-T is an incurable disease. Most children with A-T depend on wheelchairs by the age of ten because of a lack of muscle control. Children with A-T usually die from respiratory failure or cancer by their teens or early 20s. However, some patients with A-T may live into their 40s, although they are extremely rare.

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A-T Children's Project. 668 South Military Trail, Deerfield Beach, FL 33442. (800) 5-HELP-A-T. <http://www.atcp.org>.

A-T Medical Research Foundation. 5241 Round Meadow Rd., Hidden Hills, CA 91302. <http://pathnet.medsch.ucla.edu/people/faculty/gatti/gatsign.htm>.

National Ataxia Foundation. 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447. (763) 553-0020. Fax: (763) 553-0167. naf@ataxia.org. <http://www.ataxia.org>.

National Organization to Treat A-T. 4316 Ramsey Ave., Austin, TX 78756-3207. (877) TREAT-AT. <http://www. treat-at.org>.

Genevieve T. Slomski, PhD

Attention deficit hyperactivity disorder

Definition

Attention deficit hyperactivity disorder, or ADHD, is a behavioral disorder, characterized by poor attention, inability to focus on specific tasks, and excessive activity. ADHD is thought to have a strong genetic component, although studies are still ongoing to determine what role specific genes play in ADHD.

Description

Attention deficit hyperactivity disorder (ADHD) was first described by a pediatrician, Dr. George Still, in 1902. At the time, he gave an account of 43 children who exhibited such symptoms as aggressiveness, defiance, and limited attention spans. He stated that he felt these symptoms indicated a lack of "moral control" in these children and others exhibiting similar characteristics.

Until the 1950s, it was felt that the symptoms of ADHD were caused by either infections, toxins, or trauma to the head. During that time, ADHD was referred to as "minimal brain damage," or minimal brain dysfunction." In the 1960s and 1970s, when more was learned about brain functioning, scientists and doctors changed the name of the disorder to "hyperkinetic reaction to childhood" in response to the recognition of the prominent role of hyperactivity with the disorder. It was also during this time that the use of stimulants such as amphetamines began to be used to treat children diagnosed with the disorder. The term "attention deficit disorder," and finally, attention deficit hyperactivity disorder, was applied to the disorder in the 1980s and 1990s.

From the time it was first clinically described by Dr. Still, the diagnosis of ADHD has included certain basic

KEY TERMS

Allele—One of two or more alternate forms of a gene.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Dopamine—A neurochemical made in the brain that is involved in many brain activities, including movement and emotion.

characteristics, such as easy distractibility, hyperactivity, impulsivity, and a short attention span, especially when related to specific tasks. Early in its history, ADHD was thought of as a purely childhood disorder; however, it is now recognized that ADHD can continue well into adulthood. Current studies indicate that ADHD affects between six and nine million adults in the United States and is seen in both males and females, with males having the condition about twice as often as females.

Genetic profile

There is good evidence to suggest that genetic factors play an important role in ADHD. From early studies to the present, it has been recognized that ADHD tends to run in families. Multiple studies have shown that patients who have first or second degree relatives with ADHD are at higher risk for developing ADHD then patients who do not have close relatives with the condition. It has also been shown that children who are adopted are at higher risk for ADHD if their biologic parents have the condition, rather than their adoptive parents. Children whose parents have ADHD have a 50% chance of developing the condition.

While genetics certainly plays a role in ADHD, the specific genes responsible for the condition have yet to be identified. In 1993, a study reported that ADHD was seen in 40% of adults and 70% of children in a rare thyroid autosomal dominant disorder located on chromosome 3. However, later studies have been unable to confirm this initial study.

More convincing research points to a particular form of a **gene** called DRD4-7, which codes for dopamine transport in the brain. Dopamine is one of several very important brain neurotransmitters, and a certain type, or allele of DRD4-7 is thought to decrease the amount of dopamine in the brain. Studies have shown that about 30% of patients with ADHD have this certain DRD4-7 allele. In people who do not have ADHD, this allele is only seen about 15% of the time.

Demographics

Studies on the occurrence of ADHD within different ethnic, racial, and sociological groups is somewhat limited. Early studies pointed to families on the lower end of the socioeconomic scale and minority racial groups as having a higher incidence of ADHD. However, later studies have not bore these studies out, and in fact there was obvious ethnic and racial bias built into these initial studies.

More recent studies have focused on possible enviromental factors in the development of ADHD. Childhood exposure to certain toxins, such as lead, alcohol, and cigarette smoke, seemed to be linked to a higher occurrence of ADHD. Other studies point to childhood hypersensitivity to certain food additives as a contributing factor in the development of ADHD. Nutritional deficiencies in iron, zinc, and essential fatty acids have also been implicated in ADHD, but studies in this area are limited.

Signs and symptoms

ADHD is a condition defined by behaviors rather than specific chemical or genetic abnormalities. Therefore, there are very specific signs and symptoms that must be seen in a patient for a diagnosis of ADHD to be given. According to the DSM-IV (the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition), patients must show six of the following symptoms for a period of six months in order to be properly diagnosed with ADHD: failure to pay attention to details or making careless mistakes on a regular basis; difficulty sustaining attention to work or play activities; failure to listen when spoken to; failure to complete chores and assignments; difficulty in organizing tasks and activities; chronic forgetfulness; chronic restlessness or fidgeting; losing or forgetting important things; avoidance of tasks or work which requires sustained mental effort. It should be emphasized that since ADHD is based on certain behaviors, these behaviors can vary even in patients diagnosed with ADHD.

Diagnosis

Currently, there are no accepted or proven genetic studies to prove the existence of ADHD. The condition is diagnosed purely on certain behavioral characteristics that are long-term, excessive, and pervasive. These characteristics are listed above under signs and symptoms.

Treatment and management

The treatment and management of ADHD has significantly changed over time. Before the 1950s, behavioral therapy, such as teaching patients with ADHD how to improve their organizational skills and focus on tasks,

was the mainstay of treatment. However, with the development of medications specifically for psychiatric problems, the use of pharmacological agents has become a common treatment for ADHD.

The use of stimulant medications has been proven to decrease the symptoms of ADHD and to improve functioning in patients with the condition in about 75–90% of patients. It is thought that the stimulants work by increasing the amount of dopamine in the brain of patients with ADHD, either by decreasing the rate at which the brain breaks down normally present dopamine, or by causing an increase in the production dopamine. Other medications that are less frequently used to treat ADHD, such as antidepressants, also increase the amount of dopamine in the brain.

There are currently many different types of stimulant medication that can be used to treat ADHD, although it is thought they all work through increasing dopamine in the brain. The three most commonly used stimulants are methylphenidate, or Ritalin, amphetamines such as Dexedrine or Adderall, or Pemoline, also called Cylert.

All of the above stimulant medications share some common effects, as well as common side effects. In children with ADHD, use of stimulants causes a marked improvement in classroom behavior and performance, with an increase in goal-oriented organized behavior. There is a significant decrease in hyperactivity and impulsively, and most children report an improvement in their concentration abilities. Common side-effects of stimulants in both patients with ADHD and people without ADHD include decreased appetite, weight loss, insomnia, and in children, growth retardation.

The first-line stimulant in the treatment of ADHD is generally Ritalin, due to less side-effects, proven value in the condition, and relative safety, even in overdose cases. Dexedrine or Adderall is initially used if a stronger medication is needed or if patients do not respond well to Ritalin. Cylert is less potent then either Ritalin or Adderall or Dexedrine, so is a good choice if patients are sensitive to the effects of stimulants. Cylert also has the advantage of being taken only once a day, versus two or three times a day for the other stimulants.

Prognosis

Long-term studies examining patients who have been diagnosed with ADHD are limited. Some early studies done in the 1960s examined adults who had been diagnosed with ADHD as children. There were reports of increased rates of **alcoholism**, drug abuse, and lower socioeconomic levels among those adults who had been diagnosed with ADHD as children. These studies also stated that at least 50% of these adults still reported symptoms of ADHD, such as hyperactivity, poor impulse control, and inability to concentrate.

Students diagnosed with myopia have a difficult time concentrating for long periods of time. (*Field Mark Publications*)

Later studies reported in the 1990s have confirmed some, but not all of the same results as earlier studies. A study done in Canada followed over 100 boys who were diagnosed with ADHD for fifteen years. The study found that there were lower educational and occupational outcomes for those with ADHD as compared with children without the condition. However, there was no increase seen in alcohol or drug abuse as was seen in earlier studies.

Studies are currently being done following children with ADHD who are being treated with up-to-date pharmacological and behavioral therapy. It is hoped that with such treatment children with ADHD will have the same opportunities to achieve personal success as children without ADHD.

Resources

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Accardo, J. Pasquale, Thomas A. Blondis, Barbara Y. Whitman, and Mark A. Stein. eds. *Attention Deficits and Hyperactivity in Children and Adults* Marcel Dekker Inc., 2000.

PERIODICALS

Mercugliano, Marianne. "What is Attention-Deficit Hyperactivity Disorder?" *The Pediatric Clinics of North America* 46, no. 5 (October, 1999): 831-843.

ORGANIZATIONS

National Attention Deficit Disorder Association. 1788 Second St., Suite 200, Highland Park, IL 60035. (847) 432-ADDA.

WEBSITES

National Attention Deficit Disorder Foundation. <http://www.add.org>.

Edward R Rosick, DO, MPH, MS

Autism

Definition

Autism is a potentially severe neurological condition affecting social functioning, communication skills, reasoning, and behavior. It is considered a "spectrum disorder," meaning that the symptoms and characteristics of autism can present themselves in a variety of combinations, ranging from extremely mild to quite severe.

Description

Autism is a neurological disorder that affects a persons ability to communicate and form relationships. Individuals with autism have deficits in social interaction, communication, and understanding. Some individuals with autism have unusual repetitive behaviors such as head banging, rocking, and hand-flapping. Up to 75-80% of individuals with autism are mentally retarded. Only a small portion of this group (15-20%) have severe mental retardation. Additionally, over one-third of individuals with autism will develop seizures in early childhood or adolescence.

There is a wide degree of variability in the specific symptoms of autism. Because of this variability, autism is considered a spectrum disorder. There is no standard type or form of autism. Each individual is affected differently. This variability is reflected in some of the terms or names for autism. **Asperger syndrome** is a term used to describe individuals with autism with language skills. Pervasive developmental delay (PDD) is another term that is often used interchangeably with autism. The different terms for autism are partly due to the different individuals that first described this disorder.

Autism was first described by Leo Kanner in 1943. He observed and described a group of children with a pattern of symptoms. These children had some unique abilities and did not seem to be emotionally disturbed or mentally retarded. He invented the category Early Infantile Autism (sometimes called Kanners syndrome) to describe these children. In a strange coincidence, Hans Asperger made the same discoveries in the same year. He also described children with a unique behavioral profile and used the term Autism to describe them. His original study was in German and was not translated into English until the late 1980s. Because the children that he identified all had speech, the term Asperger syndrome is often used to label autistic children who have speech.

While the affects of this disorder may vary in intensity, all individuals with autism have deficits in three key areas—social interaction, communication, and reasoning. In addition to these neurologic problems, individuals with autism often exhibit bizarre repetitive movements such as hand flapping or head-banging. Other characteristics include a need for sameness or routine. While most individuals with autism have deficits, there are affected individuals that display unusual talents in areas such at math, music, and art. Some children have extraordinary talent in drawing and others learn to read before they learn to speak. These talents usually coexist with the other deficits of autism and are rare. They are usually referred to as *savant skills*.

Social interaction is the ability to interact—both verbally and non-verbally with other humans. Individuals with autism have problems recognizing the social cues such as facial expressions and tone of voice. Individuals with autism are often described as "being in their own world." This sense of isolation may arise from their inability to communicate effectively. They also lack the motivation for reciprocal communication.

Individuals with autism also have communication and language problems. They may or may not develop speech. Those individuals with autism that do speak use language in unusual ways. They may echo the comments of others (echolalia) or use phrases inappropriately. People with autism often use pronouns such as "I" "me" and "you" incorrectly. In addition to problems developing speech, individuals with autism have problems understanding the purpose of speech.

Individuals with autism can also have hyperacute senses. They may be very sensitive to bright lights, loud noises, or rough textures. The self-stimulating behaviors (head-banging, hand-flapping, rocking) sometimes seen in individuals with autism may be attempts to calm themselves due to overstimulation. Other characteristic behaviors can include throwing temper tantrums for no known reason and developing fixations or obsessive interests.

The cause of autism is unknown. Originally, it was hypothesized that autism was a psychological problem caused by defective parenting. This hypothesis has been discredited as scientific information about neurological differences and biologic causes for autism have emerged.

Genetic profile

No single specific **gene** for autism has been discovered. Although the exact cause of autism is unknown, it is thought that autism is due to a combination of genetic and environmental causes. This combination of causative factors is often referred to as multifactorial **inheritance**. There are probably a number of different genes as well as unknown environmental factors involved in the development of autism. Multifactorial conditions tend to run in families, but the pattern of inheritance is not as predictable as with single gene disorders. The chance of recurrence is also less than the risk for single gene disorders and is usually derived from empiric or long-term studies of a large number of families.

There are two separate genetic aspects of autism—studies that suggest a genetic component to autism and genetic syndromes that can cause autistic like behaviors.

There are a number of scientific studies that suggest autism is partially due to genetic causes. Twin studies are used to determine the degree of heritability of a disorder. Identical twins have the exact same genes and fraternal (non-identical) twins have only half of their genes in common. By examining the rates of concordance (the number of twin pairs that both have autism) it is possible to determine if there is a genetic component to autism. Studies that looked at the incidence of twins with autism determined that identical twins are more likely to be concordant (both affected) with autism than fraternal twins. This means that individuals with the same genes both have autism more often than twins with only half of the same genes. This finding suggests that genes play a role in the development of autism.

Identical twin pairs with autism reveal that there is a genetic component to autism. However, if autism was purely genetic, then all identical twins should be affected with autism (concordant). The fact that there are some identical twin pairs that are discordant for autism (one twin has autism and the other does not) means that other factors, possibly environmental, must also play a role in causing autism. These discordant identical twin pairs highlight the fact that there must be other factors besides genes that also influence the development of autism.

There have been speculations as to what other factors might influence or cause an individual to become autistic. These speculations include viral, immunologic (including vaccinations), and environmental factors. While there are many theories about possible causes for autism, as of 2001 no specific non-genetic causes have been found and there is no scientific evidence for any specific environmental factor being a causative agent. Much work is being done in this area.

Other scientific studies that point to the role of genes in the cause of autism are studies that look at the recurrence risk for autism. A recurrence risk is the chance that the same condition will occur for a second time in the same family. If a disease has no genetic component, then the recurrence risk should equal the incidence of the disorder. If autism had no genetic component, then it would not be expected to occur twice in the same family. However, studies have shown that autism does have an increased recurrence risk. In families with an affected son, the recurrence risk to have another child with autism is 7%. In families with an autistic daughter, the recurrence risk is 14%. In families with two children with autism, the chance that a subsequent child will also be affected is around 35%. The fact that the recurrence risks are increased in families with one child with autism indicates that there is some genetic component to autism.

KEY TERMS

Asperger syndrome—A term used to describe high-functioning individuals with autism. These individuals usually have normal IQ and some language skills.

Pervasive developmental disorder (PDD)—The term used by the American Psychiatric Association for individuals who meet some but not all of the criteria for autism.

Savant skills—Unusual talents, usually in art, math or music, that some individuals with autism have in addition to the deficits of autism.

Genetic syndromes with autistic behaviors

While no specific gene has been found to cause isolated autism, there are some genetic syndromes in which the affected individual can have autistic behaviors. These genetic syndromes include untreated **phenylketonuria (PKU)**, **Fragile X syndrome**, **tuberous sclerosis**, **Rett syndrome** and others.

Phenylketonuria is an inborn error of metabolism. Individuals with PKU are missing an enzyme necessary to break down phenylalanine, an amino acid found in protein rich food. As these individuals eat protein, phenylalanine builds up in the bloodstream and nervous system eventually leading to mental retardation and autistic behaviors. The vast majority of infants in the US are tested at birth (newborn screening) and those affected with PKU are treated with a protein free diet. This disorder is more common among individuals of northern European descent.

Fragile X syndrome is a mental retardation syndrome that predominantly (but not exclusively) affects males. Males with fragile X syndrome have long narrow faces, large cupped ears, enlarged testicles as adults and variable degrees of mental retardation. Some individuals with fragile X syndrome also display autistic behaviors.

Tuberous sclerosis is a variable disease characterized by hypopigmented skin patches, tumors, seizures, and mental retardation in some affected individuals. Up to one-quarter (25%) of individuals with tuberous sclerosis have autism.

Rett syndrome is a progressive neurological disorder that almost exclusively affects females. Girls with Rett syndrome develop normally until the age of 18 months and then undergo a period of regression with loss of speech and motor milestones. In addition, girls with Rett syndrome exhibit a nearly ceaseless hand washing or hand wringing motion. Girls with Rett syndrome also have mental retardation and can have autistic like behaviors.

While individuals with these genetic syndromes can have autistic behaviors, it is important to remember that 70–90% of individuals with autism do not have an underlying genetic syndrome as the cause of their disorder. Many studies are underway to try and determine the etiology or cause of autism.

Demographics

The exact incidence of autism is not known. Because the diagnostic criteria for autism has changed and broadened over the years, studies done to determine the incidence have yielded different estimates. Using the newer, more inclusive criteria, it is estimated that one in 500 individuals are affected with autism and that over half a million individuals in the United States fit the diagnostic criteria for autism, PDD, or Asperger syndrome.

Boys are affected three times more often than girls, giving autism a 4:1 ratio of affected boys to affected girls. While boys may be affected more often, girls with autism tend to be more severely affected and have a lower IQ. The reasons for these differences are not known. Autism occurs in all racial, social and economic backgrounds.

Signs and symptoms

One of the most frustrating aspects of autism is the lack of physical findings in individuals with autism. Most individuals with autism have normal appearance and few, if any, medical problems. Because the specific cause of autism is unknown, there is no prenatal test available for autism.

Autism is a spectrum disorder. A spectrum refers to the fact that individuals with a diagnosis of autism can have very different abilities and deficits. The spectrum of autism stretches from a socially isolated adult with normal IQ to a severally affected child with mental retardation and behavioral problems. The following is a partial list of behaviors seen in individuals with autism divided into main areas of concern. It is unlikely that any specific individual would exhibit all of the following behaviors. Most affected individuals would be expected to exhibit some but not all of the following behaviors.

Communication:

- Language delay or absence
- Impaired speech
- Meaningless repetition of words or phrases
- Communicates with gestures rather than words
- Concrete or literal understanding of words or phrases
- Inability to initiate or hold conversations

Social Interaction:

- Unresponsive to people
- Lack of attachment to parents of caregivers
- Little or no interest in human contact
- Failure to establish eye contact
- Little interest in making friends
- Unresponsive to social cues such as smiles or frowns

Play:

- Little imaginative play
- Play characterized by repetition (e.g. endless spinning of car wheels)
- No desire for group play
- No pretend games

Behaviors:

- Repetitive motions such as hand flapping and head-banging
- Rigid or flaccid muscle tone when held
- Temper tantrums or screaming fits
- Resistance to change
- Hyperactivity
- Fixates or develops obsessive interest in an activity, idea, or person
- Over reaction to sensory stimulus such as noise, lights, and texture
- Inappropriate laughing or giggling

Diagnosis

There is no medical test like a blood test or brain scan to diagnose autism. The diagnosis of autism is very difficult to make in young children due to the lack of physical findings and the variable behavior of children. Because the primary signs and symptoms of autism are behavioral, the diagnosis usually requires evaluation by a specialized team of health professionals and occurs over a period of time. This team of specialists may include a developmental pediatrician, speech therapist, psychologist, geneticist and other health professionals. Medical tests may be done to rule out other possible causes and may include a hearing evaluation, chromosome analysis, DNA testing for specific **genetic disorders** and brain imaging (MRI, EEG or CT scan) to rule out structural brain anomalies.

Once other medical causes have been excluded, the diagnosis for autism can be made using criteria from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV). This manual developed by the American Psychiatric Association lists abnormal

behaviors in three key areas—impairment in social interaction, impairment in communication (language), and restrictive and repetitive patterns of behavior—that are usually seen in individuals with autism. If an individual displays enough distinct behaviors from the following list, then they will meet the diagnostic criteria for autism. Most individuals will not exhibit all of the possible behaviors listed and while individuals might exhibit the same behaviors, there is still a large degree of variability within this syndrome.

DSM-IV criteria for autistic disorder

A. A total of at least six items from (1), (2), and (3), with at least two from (1), and one from (2) and (3):

   1. Qualitative impairment in social interaction, as manifested by at least two of the following:
      - Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
      - Failure to develop peer relationships appropriate to developmental level
      - Markedly impaired expression of pleasure in other people's happiness.
   2. Qualitative impairments in communication as manifested by at least one of the following:
      - Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gestures or mime)
      - In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
      - Stereotyped and repetitive use of language or idiosyncratic language
      - Lack of varied spontaneous make-believe play or social imitative play appropriate to developmental level.
   3. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by as least one of the following:
      - Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
      - Apparently compulsive adherence to specific nonfunctional routines or rituals
      - Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
      - Persistent preoccupation with parts of objects.

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age three years:
   1. social interaction,
   2. language as used in social communication, or
   3. symbolic or imaginative play.

C. Not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Using these criteria, the diagnosis of autism is usually made in children around the age of two and a half to three originally seen for speech delay. Often these children are initially thought to have hearing impairments due to their lack of response to verbal cues and their lack of speech.

While speech delay or absence might be the factor that initially brings a child with autism to the attention of medical or educational professionals, it soon becomes apparent that there are other symptoms in addition to the lack of speech. Children with autism are often described as "being in their own world." This can be due to their lack of spontaneous play and their lack of initiative in communication. These deficits become more obvious when children with autism are enrolled in school for the first time. Their inability to interact with their peers becomes highlighted. Behaviors such as hand flapping, temper tantrums, and head banging also contribute to the diagnosis.

Because the criteria to diagnose autism are based on observation, several appointments with healthcare providers may be necessary before a definitive diagnosis can be reached. The specialist usually closely observes ad evaluates the child's language and social behavior. In addition to observation, structured interviews of the parents are also used to elicit information about early behavior and development. Sometimes these interviews may be supplemented by review of family movies and photographs.

Many parents find the process of diagnosing autism frustrating due to the amount of time it takes and the uncertainty of the diagnosis. Many health care providers hesitate to give a diagnosis of autism and use other terms as a means of protecting the family from what they perceive to be a devastating diagnosis. While meaning well, this strategy usually increases frustration and only ultimately delays the diagnosis. The delay in diagnosis can lead to a delay in treatment and in a worse case scenario a denial of services (especially if another term is used).

Treatment and management

There is no cure for autism. However, autism is not a static disorder. Behaviors can and do change over time and educational treatments can be used to focus on appropriate behaviors. The treatments available for individuals with autism depend upon their needs, but

are generally long and intensive. While treatments vary and there is considerable controversy about some treatments, there is uniform agreement that early and intensive intervention allows for the best prognosis. A treatment plan is usually based upon an evaluation of the child's unique abilities and disabilities. A child's abilities are capitalized on in developing the treatment for their disabilities.

Standardized testing instruments are used to determine the child's level of cognitive development and interviews with parents and caregivers, as well as observation by health professionals, are used to gauge a child's social, emotional, and communication skills. Once a clear picture of the child's needs is developed, treatment is initiated. Studies have shown that individuals with autism respond well to a highly structured, specialized education program tailored to their individual needs. All treatments are best administered by trained professionals. Treatment may include speech and language therapy to develop and improve language skills. Occupational therapy may be used to develop fine motor skills and to teach basic self-help and functional skills such as grooming. Behavior modification, with positive reinforcement, plays a large role in the early treatment of some of the abnormal behaviors of individuals with autism. Other therapies may include applied behavioral analysis, auditory integration training, dietary interventions, medications, music therapy, physical therapy, sensory integration, and vision therapy.

In order to be effective, the treatments and therapies must be consistent and reinforced by the family. It is helpful if family members and caregivers also receive training in working with and teaching individuals with autism. A team approach involving healthcare professionals, therapists, educators, and families is necessary for successful treatment of individuals with autism.

Prognosis

The prognosis for individuals with autism is variable but much brighter than it was a generation ago. In general, the ultimate prognosis of an individual with autism is dependant on their overall IQ, the communicative abilities and the extent of their behavioral problems.

Individuals with autism without mental retardation can develop independent living skills. Often these individuals do well and can become self-sufficient if they have good communication skills. Other individuals with autism develop some level of self-sufficiency but may never be able to live independently due to their severe communication or cognitive difficulties. Up to 60% of individuals with autism will require lifelong assistance.

Individuals with autism and intellectual deficits (mental retardation) usually do not achieve the ability to function independently. They may require sheltered living arrangements in settings equipped to deal with their specific needs. Those individuals with autism that have severe behavioral problems will are also likely to need a supervised living arrangement.

Resources

BOOKS

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Siegel, Byrna. *The World of the Autistic Child: Understanding and Treating Spectrum Disorders*, Oxford University Press, 1998.

ORGANIZATIONS

Association for Science in Autism Treatment. 175 Great Neck Road, Suite 406, Great Neck, NY 11021. (516) 466-4400. Fax: (516) 466-4484. asat@autism-treatment.org.

Autism Society of America. 7910 Woodmont Ave. Suite 300, Bethesda, MD 20814-3015. (301) 657-0881 or (800) 3-AUTISM. <http://www.autism-society.org>.

Cure Autism Now (CAN) Foundation. 5455 Wilshire Blvd. Suite 715, Los Angeles, CA 90036-4234. (500) 888-AUTISM. Fax: (323) 549-0547. info@cureautismnow.org. <http://www.cureautismnow.org>.

National Alliance for Autism Research (NAAR). 414 Wall Street Research Park, Princeton, NJ 08540. (609) 430-9160 or (888) 777-6227 CA: (310) 230-3568. Fax: (609) 430-9163. <http://www.naar.org>.

WEBSITES

The Autism Society of America. <http://www.autism-society.org>.

OASIS Online Asperger Syndrome Information Society. <http://www.udel.edu/bkirby/asperger/>.

www.autism-resources.com. Information and links regarding the developmental disabilities autism and Asperger's syndrome. <http://www.autism-resources.com>.

The Autism/PDD Network. <http://www.autism-pdd.net/>.

The National Institute of Mental Health. <http://www..nimh.nih.gov/publicat/autism.cfm>.

Kathleen Fergus, MS, CGC

Autistic disorder *see* **Autism**

Autosomal dominant hearing loss *see* **Hereditary hearing loss and deafness**

Autosomal recessive hearing loss *see* **Hereditary hearing loss and deafness**

Azorean disease

Definition

Azorean disease causes progressive degeneration of the central nervous system. Affected individuals experience deterioration in muscle coordination and other physical symptoms, but intelligence and mental function remain unaffected by the disease.

Description

Azorean disease is an inherited disorder that causes impaired brain functioning, vision problems, and loss of muscle control. It is named for the Azores, the group of nine Portuguese islands where the disease is prevalent. Many of the reported cases have been found in the direct descendants of William Machado, an Azorean native who immigrated to the New England area of the United States, and Atone Joseph, a Portuguese sailor from the island of Flores who came to California in 1845. Other names for Azorean disease include Machado-Joseph disease, Joseph disease, and **spinocerebellar ataxia** type III.

Azorean disease is classified into three types depending on the age of onset and the specific physical symptoms. In type I, the age of onset is usually before age 25 and the affected individuals experience extreme muscle stiffness and rigidity. In type II, the age of onset is typically in the mid-30s, and progressive loss of muscle coordination (ataxia) occurs, resulting in the inability to walk. In type III, the average age of onset is 40 or later, and the main symptoms are weakness and loss of sensation in the legs.

The symptoms of Azorean disease result from the loss of brain cells and the impairment of neurological connections in the brain and spinal cord. This degradation of the central nervous system is believed to be caused by the production of a destructive protein from a mutated **gene**.

Genetic profile

Azorean disease is inherited as an autosomal dominant trait. This means that only one parent has to pass on the **gene mutation** in order for the child to be affected with the syndrome.

Each gene in the human body is made up of units called nucleotides, abbreviated C (cytosine), A (adenine), T (thymine), and G (guanine). A sequence of three nucleotides is called a trinucleotide. Azorean syndrome is caused by a genetic mutation that results in the overduplication of a CAG trinucleotide sequence. The location of the mutant gene in Azorean disease is 14q32, on the long arm of chromosome 14. This gene normally encodes the formation of a cellular protein called ataxin-3. In the general population, there are between 13 and 36 repeats of the CAG sequence, but in those individuals with Azorean disease, there may be between 61 and 84 repeats. The increased number of repetitions causes the gene to encode an abnormal protein product that is believed to cause cell death in the brain and spinal cord.

In successive generations, the number of the repetitions may increase, a phenomenon known as genetic anticipation. In addition, there appears to be a strong relationship between the number of repetitions and the age at onset of Azorean disease: the more repetitions, the sooner the disease presents and the more serious the symptoms are. Also, if the individual is homozygous for the mutated gene, meaning he or she inherits the gene from both parents, Azorean disease is more severe and the age of onset is as early as 16 years.

Demographics

Azorean disease is primarily found in people of Portuguese ancestry, particularly people from the Azores islands. In the Azores islands the incidence of Azorean disease is approximately one in every 4,000, while among those of Azorean descent, it is one in every 6,000. Azorean disease has also been identified in other ethnic groups, including Japanese, Brazilians, Chinese, Indians, Israelis, and Australian aborigines.

Signs and symptoms

The age of onset of Azorean disease is typically from the late teens to the 50s, although onset as late as the 70s has been reported. The first observable symptoms are difficulty in walking and slurred speech. There is wide variation in the range of observed symptoms, but they typically include problems with muscular coordination, eyes and vision, and other physical bodily functions such as speech and urination. Mental ability is not impaired by Azorean disease.

Muscular symptoms

Muscular symptoms observed in people with Azorean disease include:

- difficulty in walking, including staggering or stumbling,
- weakness in arms or legs,
- involuntary jerking or spastic motions,
- cramping or twisting of the hands and feet,
- facial tics and grimaces,
- twitching or rippling of the muscles in the face.

KEY TERMS

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Genetic anticipation—The tendency for an inherited disease to become more severe in successive generations.

Homozygous—Having two identical copies of a gene or chromosome.

Nucleotides—Building blocks of genes, which are arranged in specific order and quantity.

Trinucleotide—A sequence of three nucleotides.

Eyes and vision

People with Azorean disease may experience double vision, bulging eyes, difficulty in looking upward, difficulty in opening the eyes, a fixed or staring gaze, or involuntary eye movements from side to side.

Other symptoms

Other symptoms reported in people with Azorean disease include difficulty in speech such as slurring, loss of feeling in arms or legs, frequent urination, infections of the lungs, diabetes, weight loss, and difficulty sleeping.

Diagnosis

Azorean disease can be diagnosed after observation of typical symptoms and a medical history that establishes a familial pattern to the disease. Brain imaging studies such as computerized tomography (CT) and magnetic resonance imaging (MRI) may be employed. Blood tests can show increased levels of blood sugar and uric acid. Genetic studies that reveal the presence of the increased number of CAG trinucleotide repeats in the affected individual will provide definite confirmation of the diagnosis of Azorean disease.

The symptoms of Azorean disease are similar to other degenerative neurological conditions such as **Parkinson disease**, **Huntington disease**, and multiple sclerosis. Careful diagnosis is required in order to distinguish Azorean disease from these other conditions.

Treatment and management

Treatment for Azorean disease is based on management of the symptoms. As of 2001 there is no treatment that stops or reverses the effects of the disease itself. A multidisciplinary team of specialists in neurology, ophthalmology, and endocrinology is often called for. Medications that specifically treat movement disorders, such as dopamine agonists, may help alleviate some of the symptoms of Azorean disease. Some experimental drugs and treatments under development for other neurological disorders may also benefit patients with Azorean disease.

Since Azorean disease is an inherited disorder, **genetic counseling** is recommended for people with a family history of the disease.

Prognosis

The prognosis for individuals with Azorean disease varies depending on the age of onset and severity of the symptoms. The muscular degeneration caused by the disease usually results in eventual confinement to a wheelchair. After onset of the symptoms, life expectancy ranges from 10 to 30 years.

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Ataxia MJD Research Project, Inc. 875 Mahler Rd., Suite 161, Burlingame, CA 94010-1621. (650) 259-3984. Fax: (650) 259-3983. <http://www.ataxiamjd.org>.

International Joseph Disease Foundation, Inc. PO Box 2550, Livermore, CA 94551-2550. (925) 461-7550. (925) 371-1288. <http://www.ijdf.net>.

MJD Family Network Newsletter. c/o Mike and Phyllis Cote, 591 Federal Furnace Rd., Plymouth, MA 02360-4761.

National Ataxia Foundation. 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447. (763) 553-0020. Fax: (763) 553-0167. naf@ataxia.org. <http://www.ataxia.org>.

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Paul A. Johnson

B

Bardet-Biedl syndrome

Definition

Bardet-Biedl syndrome (BBS) is a condition that primarily affects vision, kidney function, limb development, growth, and intelligence.

Description

BBS expresses itself differently from person to person, even among members of the same family. However, certain features frequently appear.

Genetic profile

BBS is a genetically heterogeneous condition; this means that it has more than one known genetic cause. One of these causes is a mutation in the MKKS **gene**, located on chromosome 20. When working properly, this gene appears to produce a chaperonin, a factor needed to process proteins. Without the chaperonin, the proteins cannot work properly.

Using linkage analysis, researchers have connected some BBS cases to other **chromosomes**. Linkage analysis is a method of finding mutations based on their proximity to previously identified genetic landmarks. As of February 2001, the specific genes responsible for these BBS cases remain unknown. However, several potential locations of BBS genes have been recognized. These sites are named for the number of the chromosome on which they are found, the arm of the chromosome ("q" for long arm, "p" for short arm), region of the arm, and band within the region. For example, "11q13" means chromosome number 11, long arm, region 1, band 3. In studies of families with BBS, researchers have found that a significant number of cases link either to 11q13, 15q22, or 16q21. In other families, researchers have linked BBS to either 2q31, 3p12, or 20p12. This last site is the location of the MKKS gene.

Regardless of the site involved, BBS displays an autosomal recessive **inheritance** pattern. This means that the condition occurs only when an individual inherits two defective copies of a BBS gene. If one copy is normal, the individual does not have BBS. This individual is called a carrier of BBS and can pass the gene on to the next generation.

Research indicates that people who inherit one abnormal BBS gene and one normal gene may be at risk for some of the health problems seen in BBS. Compared to the general population, these BBS gene carriers are more likely to develop high blood pressure, **diabetes mellitus**, and kidney disease, including kidney cancer.

Demographics

BBS affects people around the world. However, it is most common in the Middle East, especially in the Arab and inbred Bedouin populations of Kuwait. In these groups, it may affect as many as one in 13,500 individuals. The incidence is almost as high in Newfoundland, where as many as one in 16,000 individuals has BBS. Outside of these areas, researchers estimate that BBS affects only one in 160,000 people.

The specific genetic cause of BBS differs by family and geographic location. For example, in the Middle East, BBS appears to link to 16q21 or 3p12. However, in patients of European descent, BBS appears to link to 11q13 or 15q22.

Signs and symptoms

If the newborn with BBS has finger or toe abnormalities, these are apparent at birth. However, these defects have a variety of congenital causes, meaning they originated during development of the fetus and were not inherited. For this reason, medical care providers may not immediately suspect BBS. It becomes a consideration as the child develops and additional abnormalities emerge. In boys, genital abnormalities become evident soon after birth. In almost all patients, obesity and retinal degenera-

KEY TERMS

Brachydactyly—Abnormal shortness of the fingers and toes.

Electroretinogram (ERG)—A measurement of electrical activity of the retina.

Intravenous pyelogram—An x ray assessment of kidney function.

Linkage analysis—A method of finding mutations based on their proximity to previously identified genetic landmarks.

Polydactyly—The presence of extra fingers or toes.

Retinitis pigmentosa—Degeneration of the retina marked by progressive narrowing of the field of vision.

Syndactyly—Webbing or fusion between the fingers or toes.

tion begin in early childhood. Learning disabilities, if present, are identified in school-aged children, if not earlier. Failure to menstruate leads to diagnosis of some adolescent girls. Infertility brings some young adults to medical attention. Kidney disease is progressive and may not become obvious until adulthood.

Due to progressive degeneration of the retina, vision damage occurs in all patients. Specific vision defects include poor night vision during childhood, severe **myopia** (nearsightedness), **glaucoma**, and cataracts. A few patients suffer from **retinitis pigmentosa**, a condition in which the field of vision progressively narrows. Most individuals affected with BBS are blind by age 30.

Many infants with BBS are born with a kidney defect affecting kidney structure, function, or both. The specific abnormality varies from patient to patient and may be aggravated by lifelong obesity, another common problem for BBS patients. The complications of obesity, such as high blood pressure (hypertension) and insulin-resistant diabetes mellitus, contribute to kidney disease.

BBS patients may have extra fingers or toes (polydactyly), short fingers (**brachydactyly**), or broad, short feet. Some patients have a combination of all three of these features. Alternately, polydactyly may be limited to one limb, hands only, or feet only. Syndactyly, the fusion of two or more fingers or toes, may also occur. In some BBS families, all affected members display at least some of these limb abnormalities.

Many individuals with BBS have genital abnormalities. Most boys with BBS have a very small penis and some also have undescended testes. Men with BBS are usually unable to have children. In women with BBS, the genitalia, ovaries, fallopian tubes, and uterus may or may not be underdeveloped. The vagina may not be completely formed. Though some women with BBS do not menstruate, others menstruate irregularly, and some women are able to have children. In both sexes, there may be birth defects in the urinary or gastrointestinal tract.

Some research indicates that people with BBS have characteristic facial features, including a prominent forehead, deep-set eyes, flat nasal bridge, and thin upper lip. Teeth are small and crowded, and a high, arched palate is common.

Occasionally, individuals with BBS have liver disease or heart abnormalities.

In addition to the physical effects of the condition, intelligence is sometimes affected. While some BBS patients show normal intelligence, others have mild to moderate learning disabilities. These patients are often developmentally delayed—they are slower than most children to walk, speak, or reach other developmental milestones. Difficulty with language and comprehension may continue into adulthood. In a few people with BBS, more severe mental retardation occurs. In some patients, vision handicap and developmental delay appear to be related.

Some parents report that their children with BBS have behavioral problems that continue into adulthood. These include lack of inhibition and social skills, emotional outbursts, and obsessive-compulsive behavior. Most people with BBS prefer fixed routines and are easily upset by a change in plans.

Diagnosis

Diagnosis of BBS is a challenge for medical professionals. Not only do the symptoms of BBS vary greatly from patient to patient, but some of these symptoms occur in other conditions, many of which are more common than BBS.

Though available on a research basis, **genetic testing** for BBS is not yet offered through clinical laboratories. Instead, it is the association of many BBS symptoms in one patient that generally leads to a clinical diagnosis. Therefore, patients must have a thorough genetic evaluation. This provides a chance to rule out other disorders with similar symptoms. Because symptoms emerge throughout childhood, patients diagnosed as infants require regular exams to confirm proper diagnosis. Some disorders historically confused with BBS include Lawrence-Moon syndrome, Kearns-Sayre syndrome, and **McKusick-Kaufman syndrome**. This last syndrome is also caused by mutation in the MKKS gene; in fact, the

gene took its name from McKusick-Kaufman syndrome. While people with this syndrome show some of the same symptoms as BBS patients, the specific MKKS mutation differs between the conditions. This explains how one gene can be responsible for two distinct yet similar disorders.

Six major criteria form the basis of BBS diagnosis. These are retinal degeneration, polydactyly, obesity, learning disabilities, kidney abnormalities, and genital defects (in males). To confirm diagnosis, the patient should receive three particular diagnostic tests. An eye exam called an electroretinogram is used to test the electric currents of the retina. An ultrasound is used to examine the kidneys, as is an intravenous pyelogram (IVP). An IVP is an x-ray assessment of kidney function.

Treatment and management

Unless they have severe birth defects involving the heart, kidneys, or liver, patients with BBS can have a normal life span. However, obesity and kidney disease are major threats. If unchecked, obesity can lead to high blood pressure, diabetes mellitus, and heart disease. Untreated kidney disease can lead to **renal failure**, a frequent cause of early death in patients with BBS. Some patients require dialysis and kidney transplant. Therefore, it is very important to monitor and manage patients with BBS, and to promptly treat any complications. Affected individuals should eat a well-balanced, low-calorie diet and exercise regularly.

Because BBS carriers also appear prone to kidney disease, parents and siblings of patients with BBS should take extra precautions. These include baseline screening for kidney defects or cancer, as well as preventive health care on a regular basis.

In order to conserve vision to the extent possible, retinal degeneration should be carefully monitored. Therapy, education, and counseling help prepare the patient for progressive loss of vision. The Foundation Fighting Blindness, a support and referral group, offers help to BBS patients and their families.

Though not life-threatening, learning disabilities and reproductive dysfunction need attention in order to maximize the quality of life for patients with BBS. Affected people benefit greatly from special or vocational education, speech therapy, social skills training, and community support services. Some adult patients may never be able to live independently and may remain with their families. In these cases, families should plan future living arrangements in case the patients outlive their caregivers.

Genital abnormalities may require hormonal treatment or surgical attention. Sometimes removal of undescended testes is necessary to prevent cancer. Patients with genital and reproductive dysfunction may need counseling to help them deal with the personal, familial, social, and cultural impact of the condition. **Genetic counseling** is available to help fertile BBS patients address their reproductive choices.

Prognosis

The outlook for people with BBS depends largely on the extent of the birth abnormalities, prompt diagnosis, and follow-up care. At this time there is no treatment for the extensive retinal damage caused by BBS. However, good health care beginning in childhood can help many people with BBS avoid other serious effects of this disorder. Researchers are actively exploring genetic causes, treatment, and management of BBS.

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ORGANIZATIONS

Foundation Fighting Blindness. Executive Plaza 1, Suite 800, 11350 McCormick Rd., Hunt Valley, MD 21031. (888) 394-3937. <http://www.blindness.org>.

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937. info@geneticalliance. <http://www.geneticalliance.org>.

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Avis L. Gibons

Batten disease

Definition

Batten disease is a disorder of the nervous system that begins in childhood. Symptoms of the disorder include mental impairment, seizures, and loss of sight and motor skills.

KEY TERMS

Lipopigments—Substances made up of fats and proteins found in the body's tissues.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Neuronal ceroid lipofuscinoses—A family of four progressive neurological disorders.

Description

Batten disease is characterized by an abnormal buildup of lipopigments—substances made up of fats and proteins—in bubble-like compartments within cells. The compartments, called lysosomes, normally take in and break down waste products and complex molecules for the cell. In Batten disease, this process is disrupted, and the lipopigments accumulate. This breakdown is genetic. It is marked by vision failure and the loss of intellect and neurological functions, which begin in early childhood.

Batten disease is a form of a family of progressive neurological disorders known as neuronal ceroid lipofuscinoses (or NCLs). It is also known as Spielmeyer-Vogt-Sjögren-Batten disease, or juvenile NCL. There are three other disorders in the NCL family: Jansky-Bielchowsky disease, late infantile neuronal ceroid lipofuscinosis, and Kufs disease (a rare adult form of NCL). Although these disorders are often collectively referred to as Batten disease, Batten disease is a single disorder.

Genetic profile

Batten disease was named after the British pediatrician who first described it in 1903. It is an autosomal recessive disorder. This means that it occurs when a child receives one copy of the abnormal **gene** from each parent. Batten disease results from abnormalities in gene CLN3. This specific gene was identified by researchers in 1995.

Individuals with only one abnormal gene are known as carriers; they do not develop the disease but can pass the gene on to their own children. When both parents carry one abnormal gene, their children have a one in four chance of developing Batten disease.

Demographics

Batten disease is relatively rare, occurring in two to four of every 100,000 births in the United States. NCLs appear to be more common in children living in Northern Europe and Newfoundland, Canada.

Signs and symptoms

Early symptoms of Batten disease include vision difficulties and seizures. There may also be personality and behavioral changes, slow learning, clumsiness, or stumbling. These signs typically appear between ages five and eight. Over time, the children experience mental impairment, worsening seizures, and the complete loss of vision and motor skills.

Batten disease, like other childhood forms of NCL, may first be suspected during an eye exam that displays a loss of certain cells. Because such cell loss can occur in other eye diseases, however, the disorder cannot be diagnosed by this sign alone. An eye specialist who suspects Batten disease may refer the child to a neurologist, who will analyze the medical history and information from various laboratory tests.

Diagnosis

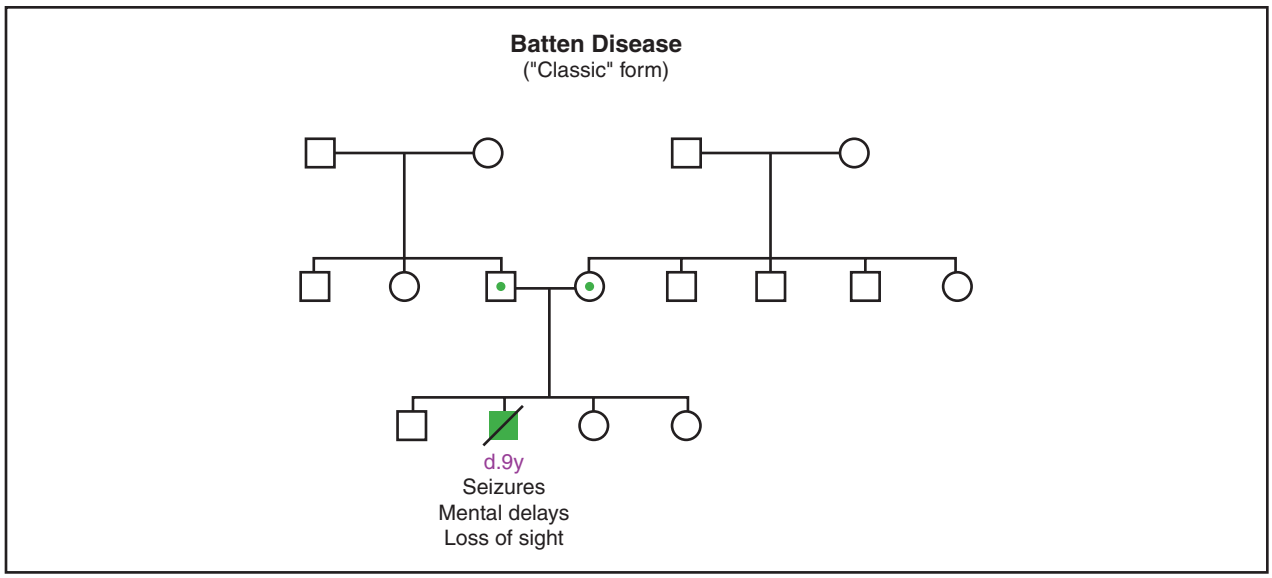
Diagnostic tests used for Batten disease and other NCLs include:

- Blood or urine tests that detect abnormalities that may indicate Batten disease
- Skin or tissue sampling, which can detect the buildup of lipopigments in cells
- Electroencephalogram, which displays electrical activity within the brain that suggests a person has seizures
- Electrical studies of the eyes that further detect various eye problems common in childhood NCLs
- Brain scans, which spot changes in the brain's appearance

Treatment and management

There is no known treatment to prevent or reverse the symptoms of Batten disease or other NCLs. Anticonvulsant drugs are often prescribed to reduce or control seizures. Other medicines may be prescribed to manage other symptoms associated with the disorder. Physical and occupation therapy may also help people retain function for a longer period of time. Scientists' recent discovery of the genes responsible for NCLs may help lead to effective treatments.

There have been reports of the slowing of the disease among children who were given vitamins C and E and diets low in vitamin A. However, the fatal outcome of the disease remained the same.



(Gale Group)

Prognosis

People with Batten disease may become blind, confined to bed, and unable to communicate. Batten disease is typically fatal by the late teens or 20s. Some people with the disorder, however, live into their 30s.

Resources

ORGANIZATIONS

Battens Disease Support and Research Association. 2600 Parsons Ave., Columbus, OH 43207. (800) 448-4570. <http://www.bdsra.org.>.

Children's Brain Disease Foundation. 350 Parnassus Ave., Suite 900, San Francisco, CA 94117. (415) 566-5402.

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

JNCL Research Fund. PO Box 766, Mundelein, IL 60060. <http://www.jnclresearch.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Michelle Lee Brandt

BBB syndrome *see* **Opitz syndrome**

Beals syndrome

Definition

Beals syndrome, also known as Beals contractural arachnodactyly (BCA), congenital contractural arachnodactyly, or Beals-Hecht syndrome, is a rare genetic disorder that involves the connective tissue of the skeleton.

Description

Individuals diagnosed with Beals syndrome usually have long, thin, fingers and toes that cannot be straightened out because of contractures, meaning a limited range of motion in the joints of their fingers, hips, elbows, knees, and ankles. They also have unusual external ears that appear crumpled. Contractures of the elbows, knees, and hips at birth are very common. Some babies also have **clubfoot**, causing one or both feet to be turned in towards each other at the ankles. In most individuals, the contractures improve with time and the clubfoot responds well to physiotherapy.

The condition occurs when fibrillin, an important component of the body's connective tissue (the glue and scaffolding of the body; for example bones, cartilages,

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Fibrillin-2—A protein that forms part of the body's connective tissue. The precise function of fibrillin-2 is not known.

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Mitral valve prolapse—A heart defect in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur but there are usually no symptoms.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Scoliosis—An abnormal, side-to-side curvature of the spine.

tendons, and fibers) is not made properly by the body. The **gene** responsible for making fibrillin is called FBN2 and it is located on chromosome 5. Any mutation (change) occurring in the FBN2 gene results in Beals syndrome.

Genetic profile

Beals syndrome is caused by a mutation occurring in a gene. Genes are units of hereditary material passed from a parent to a child through the egg and sperm. The information contained in genes is responsible for the development of all the cells and tissues of the body. Most genes occur in pairs: one copy of each pair is inherited from the egg cell produced by the mother and the other copy of each pair comes from the sperm cell of the father. One of these genes (called FBN2) tells the body how to make fibrillin-2, a specific type of protein. Proteins are substances made in the body that consist of chemicals called amino acids. Fibrillin-2 is an important part of connective tissue. Connective tissue provides structural support and elasticity to the body. It is made up of various components, including elastic-like fibers, and fibrillin-2 is thought to play a role in ensuring that the elastic fibers of the connective tissue are assembled properly early in development; however, the precise function of fibrillin-2 remains unknown. People with Beals syndrome have a mutation in one copy of their FBN2 gene. As a result, the fibrillin-2 they make is unable to work properly and this causes the BCA symptoms.

Beals syndrome is inherited as a dominant condition. In dominant conditions, a person needs to have only one altered gene copy to develop the condition. The mutation in the FBN2 gene that causes Beals syndrome can be inherited from a parent who is also affected with BCA. Individuals with Beals syndrome have a 50% chance in each pregnancy to have a child with Beals syndrome.

Sometimes Beals syndrome cannot be traced back to a parent with the condition. In these cases, the genetic change is said to be a spontaneous mutation. This means that some unknown event has caused the FBN2 gene (which functions normally in the parent) to mutate in either the sperm of the father or the egg of the mother. If fertilization occurs, the resulting individual will have Beals syndrome. A person who has Beals syndrome due to a spontaneous mutation can then pass on this altered FBN2 gene to his or her future children.

Demographics

Beals syndrome affects males and females of all ethnic groups. It is a rare condition and accurate estimates of the number of affected people are not available.

Signs and symptoms

Besides the general appearance displayed by persons with Beals syndrome (tall and thin, contractures, with typical crumpled ear), symptoms of the disorder vary from one affected individual to the next. Sometimes,

arms are disproportionately long for the height of the person. Other less common features may include a small chin, protruding forehead, and a high arch in the roof of the mouth (palate).

An abnormal bending or twisting of the spine (kyphosis/scoliosis) is seen in about half of individuals diagnosed with Beals syndrome and can occur in early infancy. This bending and twisting of the spine tends to worsen over time. Some individuals may also have an abnormal indentation or protrusion of their chest wall. Decreased muscle bulk, especially in the lower legs, is also a common sign of Beals syndrome.

Less common symptoms of Beals syndrome include heart and eye problems. The most frequent heart problem involves one of the heart valves (mitral valve prolapse) and may necessitate medication prior to dental or other surgeries so as to prevent infection. More serious heart problems may occur but are rare. The aorta, the major blood vessel carrying blood away from the heart, may occasionally enlarge. This condition usually requires medication to prevent further enlargement or rarely, surgery. A small number of individuals with Beals syndrome may also be nearsighted and require eye glasses.

Diagnosis

The diagnosis of Beals syndrome is based on the presence of specific conditions. The diagnosis is suspected in anyone with the typical features of Beals syndrome such as tall, slender stature, contractures of many joints including the elbows, knees, hips, and fingers, abnormal curvature of the spine, decreased muscle bulk, and crumpled ears. As of 2001, a genetic test to confirm a BCA diagnosis has yet to become routinely available. **Genetic testing** for this syndrome remains limited to a few research laboratories around the world.

Testing during pregnancy (prenatal diagnosis) to determine whether the unborn child of at-risk parents may be affected by BCA is not routinely available. Also, because of the rather mild nature of the condition in most individuals, prenatal diagnosis is usually not requested. There has been at least one documented prenatal diagnosis for Beals syndrome. Using a procedure called **amniocentesis**, fluid surrounding the developing baby was removed and cells from that fluid were submitted to genetic testing in a research laboratory. The procedure allowed confirmation that the unborn child was affected with Beals syndrome.

Treatment and management

There is no cure for Beals syndrome. Management of the disorder usually involves physiotherapy in early childhood to increase joint mobility and to lessen the effects of low muscle bulk. The contractures have been known to spontaneously improve, with surgery sometimes required to release them.

The abnormal curvature of the spine tends to worsen with time. A bone specialist should be consulted for advice on the appropriate treatment. Some individuals may require a back brace and/or surgery to correct the curvature.

A heart specialist should be consulted because some individuals with Beals syndrome have been known to have heart defects. Usually, an ultrasound of the heart is taken to assess whether there are any abnormalities. Medications may be used to treat some types of heart problems, if any. An eye specialist should also be consulted because of the possibility of eye problems such as **myopia** (nearsightedness). Prescription eye glasses may be necessary.

Individuals with Beals syndrome and their families may benefit from **genetic counseling** for information on the condition and recurrence risks for future pregnancies.

Prognosis

There tends to be gradual improvement in the joint contractures with time. The abnormal spinal curvature tends to get worse over time and may require bracing or surgery. The life span of individuals with Beals syndrome is not altered.

Resources

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AVENUES National Support Group for Arthrogryposis Multiplex Congenita. PO Box 5192, Sonora, CA 95370. (209) 928-3688. avenues@sonnet.com. <http://www.sonnet.com/avenues>.

National Marfan Foundation. 382 Main St., Port Washington, NY 11050-3121. (800) 862-7326. <http://www.marfan.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Nada Quercia, Msc, CCGC CGC

Beals-Hecht syndrome *see* **Beals syndrome**

Bean syndrome *see* **Blue rubber bleb nevus syndrome**

Beare-Stevenson cutis gyrata syndrome

Definition

Beare-Stevenson Cutis gyrata syndrome is a serious, extremely rare inherited disorder affecting the skin, skull, genitals, navel, and anus. This condition often results in early death.

Description

Beare-Stevenson cutis gyrata syndrome is also known as Beare-Stevenson syndrome and cutis gyrata syndrome of Beare and Stevenson. This very rare inherited disease causes serious physical problems affecting many body parts. Cutis gyrata is characterized by an unusual ridging pattern in the skin resembling corrugation in cardboard. This skin corrugation is present from birth and commonly occurs on the head and arms.

All people with Beare-Stevenson cutis gyrata syndrome are mentally retarded or developmentally delayed. The brain, skull, face, respiratory system, and genitals are often malformed. Death at an early age is common.

Genetic profile

Beare-Stevenson cutis gyrata syndrome is an autosomal dominant disorder, meaning that a person needs a change, or mutation, in only one of two copies of the **gene** involved to manifest the disorder. As of 2001, all reported cases have been sporadic, or random, occurrences, happening in families with no family history of the disease. This syndrome is associated with mutations in FGFR2, a fibroblast growth factor receptor gene. The fibroblast growth factor receptor genes serve as blueprints for proteins important to inhibition of cell growth during and after embryonic development. FGFR2 is located on human chromosome 10 in an area designated as 10q26.

Demographics

As of 2001, less than 10 cases of Beare-Stevenson cutis gyrata syndrome have been reported. Both males and females are affected. The few cases documented in the medical literature suggest that some cases of this disease might be associated with advanced paternal age, or older fathers.

KEY TERMS

Acanthosis nigricans—A skin condition characterized by darkly pigmented areas of velvety wart-like growths. Acanthosis nigricans usually affects the skin of the armpits, neck, and groin.

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

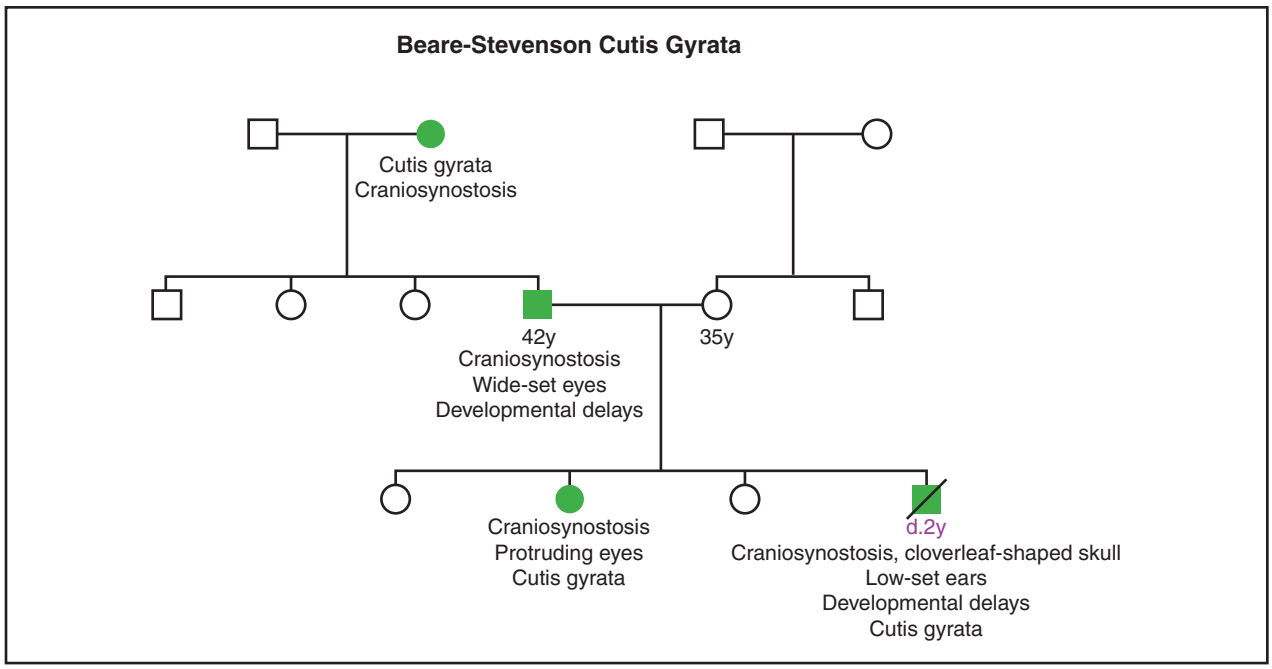
Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Signs and symptoms

All people with Beare-Stevenson cutis gyrata syndrome are developmentally delayed or mentally retarded. There may be excess fluid on the brain (**hydrocephalus**), and the nerve connection between the two halves of the brain (the corpus callosum) may be absent or underdeveloped.

A cloverleaf-shaped skull is a very unusual birth abnormality that is common in infants with Beare-Stevenson cutis gyrata syndrome. Abnormalities in skull shape happen when the sutures (open seams between the bony plates that form the skull) fuse before they typically would. Premature closure of the skull sutures is known as **craniosynostosis**. Growth of the brain pushes outward



(Gale Group)

on skull plates that have not yet fused, causing characteristic bulges in those areas.

The characteristic face of someone with Beare-Stevenson cutis gyrata syndrome has prominent, bulging eyes that slant downward with droopy eyelids. The middle third of the face is underdeveloped and may appear somewhat flattened. The ears are positioned lower and rotated backward from where they would typically be. Skin ridges may be found in front of the ear. Infants with this condition may be born with teeth.

The most recognizable physical symptom of this syndrome is the unusual ridging, or corrugation, of the skin. This cutis gyrata affects the skin on the scalp, face, ears, lips, and limbs and is usually evident at birth. Patches of skin on the armpits, neck, and groin may also display acanthosis nigricans, unusually dark, thickened patches of skin with multiple delicate growths. Skin tags may be present on the surface of the skin and on the tissues lining the mouth. Affected children usually have a prominent navel and may have extra nipples.

People with this disorder may not be able to fully straighten their arms at the elbow. The skin of the palms of the hands and the soles of the feet often show deep ridging. Affected individuals may have small, underdeveloped fingernails.

Children with Beare-Stevenson cutis gyrata syndrome may have breathing problems and narrowing of the roof of the mouth (cleft palate). The anus may be positioned more forward than normal. The genitals are often malformed and surrounded by corrugated skin. An abnormal stomach valve may cause feeding problems.

Diagnosis

Diagnosis of Beare-Stevenson cutis gyrata syndrome is based on visible hallmark characteristics of the disease. As of 2001, all reported cases have shown hallmark characteristics from birth. DNA testing is available for Beare-Stevenson cutis gyrata syndrome. This testing is performed on a blood sample to confirm a diagnosis made on physical features. Prenatal **genetic testing** is also available. Beare-Stevenson cutis gyrata may be suspected in an unborn fetus if a hallmark characteristic, like a cloverleaf skull, is visible on prenatal ultrasound.

Treatment and management

There is no cure for Beare-Stevenson cutis gyrata syndrome. Of less than 10 reported cases in the literature, many died early in life. So few people have been diagnosed with this disease that there is no published information regarding its treatment and management.

Prognosis

Early death is common in people with Beare-Stevenson cutis gyrata syndrome, especially among those with a cloverleaf skull.

Resources

PERIODICALS

Hall, B. D., et al. "Beare-Stevenson Cutis Gyrata Syndrome." *American Journal of Medical Genetics* 44 (1992): 82- 89.

Krepelova, Anna, et al. "FGFR2 Gene Mutation (Tyr375Cys) in a New Case of Beare-Stevenson Syndrome." *American Journal of Medical Genetics* 76 (1998): 362-64.

ORGANIZATIONS

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

FACES. The National Craniofacial Assocation. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

WEBSITES

"Cutis Gyrata Syndrome of Beare and Stevenson." *OMIM—Online Mendelian Inheritance in Man.* <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=123790>.

Judy C. Hawkins, MS

Becker muscular dystrophy *see* **Duchenne muscular dystrophy**

Beckwith-Wiedemann syndrome

Definition

Beckwith-Wiedemann syndrome (BWS) refers to a disorder of overgrowth. This condition is usually characterized by large body size (macrosomia), large tongue (macroglossia), enlarged internal organs (visceromegaly), the presence of an abdominal wall defect (umbilical hernia or **omphalocele**), and low blood sugar in the newborn period (neonatal hypoglycemia).

Description

Beckwith and Wiedemann initially described Beckwith-Wiedemann syndrome in the 1960s. It is also known as Wiedemann-Beckwith syndrome and exomphalos macroglossia gigantism syndrome (EMG syndrome).

BWS syndrome will frequently present prenatally with fetal macrosomia, enlarged placentas, and often more than usual amniotic fluid (polyhydramnios) that may lead to premature delivery (a baby being born more than three weeks before its due date). In the first half of pregnancy, the majority of amniotic fluid is made by the movement of sodium, chloride, and water crossing the amniotic membrane and fetal skin to surround the fetus. During the second half of pregnancy, the majority of amniotic fluid is fetal urine that is produced by the fetal kidneys. Another major source of amniotic fluid is secretion from the fetal respiratory tract. This sterile fluid is not stagnant. It is swallowed and urinated by the fetus constantly and is completely turned over at least once a day. If the fetus has an enlarged tongue (macroglossia), and cannot swallow as usual, this can lead to build-up of excess amniotic fluid. Aside from swallowing difficulties in the newborn, macroglossia can also lead to difficulties with feeding and breathing.

Approximately 75% of infants who have BWS will have an omphalocele. An omphalocele occurs when the absence of abdominal muscles allows the abdominal contents to protrude through the opening in the abdomen. This is covered by a membrane into which the umbilical cord inserts. Omphaloceles are thought to be caused by a disruption of the process of normal body infolding at three to four weeks of fetal development. Although 25% of infants with BWS do not have omphaloceles, they may have other abdominal wall defects such as an umbilical hernia or even a less severe separation of the abdominal muscles, called diastasis recti.

Fifty to sixty percent of newborns with BWS present have low blood sugar levels within the first few days of life. This is called neonatal hypoglycemia and is caused by having more than the usual number of islet cells in the pancreas (pancreatic islet cell hyperplasia). The islet cells of the pancreas produce insulin. This cluster of cells is called the islets of Langerhans and make up about 1% of the pancreas. These cells are the most important sugar (glucose) sensing cells in the body. When an individual eats a meal high in glucose or carbohydrates, this leads to a rise in blood sugar, which is then a signal for the increased insulin secretion by the islet cells of the pancreas. If too much insulin is produced, then the blood glucose levels drop too low. This is called hypoglycemia. Since glucose is the primary fuel for brain function, if hypoglycemia lasts too long, it can lead to brain damage. For this reason, detection and treatment of the hypoglycemia is extremely important. Any child born with features of this syndrome should be carefully monitored for hypoglycemia, especially during the first week of life. Occasionally, onset of hypoglycemia is delayed until the first month after birth. For this reason, the parents of a child with BWS should be taught to watch for the symptoms of hypoglycemia so that they can seek care as soon as possible.

Children with BWS have an increased risk of mortality associated with tumor development. These tumors begin development during fetal life (embryonal tumors).

These malignant tumors develop in approximately 8% of children who have BWS. The most frequently seen tumors in individuals who have BWS include Wilms tumor (nephroblastoma) and hepatoblastomas. Wilms tumor is a tumor that arises in the kidney and consists of several embryonic tissues. Wilms tumor accounts for 80% of all kidney tumors in children. The peak incidence occurs between two and three years of age, but can be present from infancy to adulthood.

Hepatoblasomas are tumors that arise in the liver during fetal development and is the most common primary liver tumor in infancy and childhood. A wide variety of other tumors, both malignant and benign, are also seen in individuals who have BWS and include, but are not limited to, nervous system tumors (neuroblastomas), adrenal gland tumors, and tumors that commonly occur in the head and neck (rhabdomyosarcoma). The increased risk for tumors appears to be concentrated in the first eight years of life, consistent with the embryonic nature of these tumors. In patients who have BWS, tumor development is not common after age eight.

Hemihyperplasia of a lower extremity or of the whole half of the body can be present. For example, one leg may be longer than the other leg. If hemihyperplasia is present, it may be recognized at birth and may become more or less obvious as a child grows. The risk of tumor development increases significantly when hemihyperplasia is present. While only 13% of affected individuals have hemihyperplasia, 40% of those with neoplasms have hyperplasia. Most patients with BWS remain at or above the 95th percentile for length through adolescence. Advanced bone age can be identified on x ray examination. Growth rate usually slows down at around age seven or eight. After nine years of age, the average weight remains between the 75th and 95th percentile. Although height, weight, skeletal, and dental maturity may be above average for years, growth rate gradually slows down and eventually children reach average height and normal proportions. Puberty occurs at a usual time.

Another feature includes unusual linear grooves within the ear lobes and/or a groove or pit on the top of the outer ear. Facial characteristics may include prominent eyes (exophthalmos), "stork bite" birth marks (telangiectatic nevi) of the upper half of the face, and "port wine stain" birth marks (facial nevus flammeus) on the face.

Genetic profile

The genetics of BWS is complex. Approximately 85% of individuals who have BWS have no family history of BWS and have a normal **karyotype**. Of these patients, approximately 20% have paternal uniparental disomy for chromosome 11p15. Uniparental disomy occurs when an individual receives two copies of a chromosome, part of a chromosome, or a **gene** from one parent, as opposed to receiving one copy from each parent. In this situation, the amount of gene expression can be changed and cause a disease or disorder. Approximately 5-10% of patients who have no family history and a normal karyotype have a gene change identified near 11p15, called p57(KIP2). This gene region, p57(KIP2), is a tumor supressor region, meaning that its presence suppresses tumor development, but that the loss of a normally functioning region could lead to tumor development and potentially lead to BWS. The IGF-2 (insulin-like growth factor-2) gene is also in this region. Both uniparental disomy and a **gene mutation** result in dosage changes of the normal functioning genes, resulting in overexpression and subsequently increased growth and tumor risk. When a gene change in the p57(KIP2) region is found in either of the parents of the affected child, the chance for a future child to have BWS could be as high as 50% with each future pregnancy. The remaining 70% of individuals who have BWS, no family history, and a normal karyotype have no identifiable cause

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Hemihyperplasia—A condition in which overdevelopment or excessive growth of one half of a specific organ or body part on only one side of the body occurs.

Neonatal—Neonatal refers to the first 28 days after birth.

Nevus flammeus—A flat blood vessel tumor present at birth, also known as a "port wine stain."

for BWS. The chance for other family members to be affected in this case is expected to be low.

Approximately 10-15% of individuals who have BWS have a positive family history and a normal karyotype. Of these families, up to 50% may have an identifiable gene change in the p57 region. If a female carries this gene change, then she has a 50% chance with each pregnancy for having a child with BWS. If a male carries the gene change, the chance for having an affected child is increased, but specific risks are not yet available. Up to 50% of individuals with a positive family history and a normal karyotype do not have an identifiable gene change in the p57 region. In this situation, the chance for the parents to have another affected child is as high as 50%.

Approximately 1-2% of patients with BWS have a detectable chromosome abnormality. In patients who have a translocation or a duplication of 11p15 detected on their karyotype, the parents' chromosome analysis should be analyzed. Depending upon the results of the parents' chromosome analysis, there could be up to a 50% chance of having an affected child with BWS.

Demographics

The reported incidence for BWS is approximately one in 14,000, although this is likely to be an underestimate because of undiagnosed cases. BWS is not found more commonly in any particular sex or geographic region and has been reported in a wide variety of ethnic backgrounds.

Signs and symptoms

Major signs or symptoms include: macrosomia, macroglossia, abdominal wall defect, visceromegaly, embryonal tumors, hemihyperplasia, ear lobe creases or ear pits, renal abnormalities, and rarely cleft palate.

Minor signs and symptoms include: polyhydramnios, prematurity, neonatal hypoglycemia, advanced bone age, heart defects, hemangioma, facial nevus flammeus, and the characteristic facial features, which include underdeveloped midface and possible soft-tissue folds under the eyes.

Diagnosis

BWS is diagnosed primarily by the identification of clinical signs and symptoms. Although there is no official diagnostic criteria for BWS, most would agree that a diagnosis requires the presence of three major findings, or at least two major findings and one minor finding. For the purposes of diagnosis, a major finding would also include a family history of BWS.

When considering the diagnosis of BWS, several other syndromes should also be considered (differential diagnosis). These include, but are not limited to, infant of a diabetic mother, **Simpson-Golabi-Behmel syndrome**, Perlman syndrome, **Sotos syndrome**, and **Costello syndrome**.

If a couple has had a child affected with BWS and an identifiable gene change in the p57 region has been identified, or if a chromosome abnormality is detected by chromosome analysis, then prenatal testing through chorionic villus sampling or **amniocentesis** is possible. If this is not possible, then potentially, detailed ultrasound examination could help to reassure parents that the signs and symptoms of BWS are not present (such as omphalocele, macroglossia, and macrosomia). If any of these signs or symptoms are present, and the couple has had a previously affected child, then it would be very likely that the present pregnancy is affected as well.

If a couple has not had a previously affected child and has had an ultrasound examination that identifies an omphalocele, then chromosome analysis should be offered to rule out a chromosome abnormality and to look for the abnormal chromosome findings associated with BWS. If chromosome results are normal, BWS is still a possible cause for the ultrasound findings.

Treatment and management

Early treatment of hypoglycemia is important to reduce the risk of central nervous system damage. Most cases of hypoglycemia are mild and will resolve shortly with treatment, however, some cases may be more difficult to treat. Treatment for hypoglycemia may include steroid therapy, which is usually required for only one to four months.

If an infant has an abdominal wall defect, such as an omphalocele, surgery is usually performed soon after birth to repair the defect. For very large omphaloceles, a multi-stage operation is performed. The treatment and management of the omphalocele depends upon the presence of other problems and is very specific to each individual.

A cardiac evaluation is recommended prior to surgery or if a heart defect is suspected by clinical evaluation. Cardiomegaly is frequently present, but usually resolves without treatment.

Non-malignant kidney abnormalities, including renal cysts and hydronephrosis, occur in approximately 25% of patients. A consult with a pediatric nephrologist would be recommended for patients who have structural renal abnormalities, including any evidence of renal calcium deposits on ultrasound examination.

To screen for tumors, a baseline magnetic resonance imaging or computed tomography (CT) examination of the abdomen is recommended for individuals believed to have BWS. To screen for Wilms tumor and other embryonal tumors, abdominal ultrasound is recommended. Blood pressure should also be monitored, as approximately 50% of people with Wilms tumors may have associated hypertension. Because tumor development may occur at any time, though usually before eight years of age, the screening recommendations are that abdominal ultrasound be performed every three to six months until eight years of age, and then annually until growth is complete. In addition to ultrasound, screening for hepatoblastoma is accomplished by serial measurements of the serum alpha-fetoprotein (AFP) levels during these years as well. Elevated levels of serum AFP are present 80-90% of the time when a hepatoblastoma is present. Alpha-fetoprotein is a protein produced by the fetal liver. Concentrations of this protein fall rapidly during the first few weeks after birth and reach adult levels by six months of age. These adult levels are approximately 2-20 ng/ml. Thus, the presence of elevated levels in children and adults usually indicates tumor development. Abnormal AFP levels should be followed with an abdominal CT examination looking for evidence of a tumor in the liver.

Surgical removal is the primary treatment for hepatoblastoma; however, in tumors that cannot be removed, chemotherapy is performed.

Treatment for Wilms tumor is often only surgical removal of the tumor; however, in some cases chemotherapy and radiation therapies are necessary, depending upon the stage of disease and the characteristics of the tumor.

Macroglossia may need to be addressed with the possibility of surgery. The large tongue may partially block the respiratory tract and lead to problems such as difficulty breathing and feeding. In most cases, the tongue growth slows over time and eventually the tongue can be accommodated. Dental malocclusion and a prominent jaw are secondary to the macroglossia. In rare cases, surgery to reduce tongue size is needed and is usually performed between two and four years of age.

Prognosis

After dealing with initial neonatal issues such as hypoglycemia, feeding, and respiratory problems, prognosis is usually good. Infants with BWS syndrome have an approximately 20% mortality rate. This is mainly due to complications stated above, and also includes complications of prematurity and omphalocele. The prognosis with repaired omphalocele is good. The majority of deaths in cases of omphalocele are usually associated with other anomalies or respiratory insufficiency. Respiratory insufficiency can occur in patients with omphaloceles if the omphalocele is so large that prenatal lung development cannot occur as usual. Respiratory insufficiency can also occur because of prematurity.

Tumor survival rates for Wilms tumor and for hepatoblastoma are as follows. In general, the four-year survival of all patients who have Wilms tumor with favorable histology approaches 90%. For hepatoblastomas, the combination of surgery and chemotherapy has achieved disease-free survival rates of 100% for stage I, 75% for stage II, and 67% for stage III hepatoblastomas.

In children who have BWS, development is usually normal if there is no history of significant, untreated hypoglycemia. After childhood, complications for patients with BWS are uncommon and prognosis is good.

Resources

BOOKS

Jones, Kenneth Lyons. *Smith's Recognizable Patterns of Human Malformation.* W.B.Saunders Company, 1997.

ORGANIZATIONS

Beckwith-Wiedemann Support Network. 2711 Colony Rd., Ann Arbor, MI 48104. (734) 973-0263 or (800) 837-2976. <http://www.beckwith-wiedemann.org>.

Renee A. Laux, MS

Berlin breakage syndrome *see* **Nijmegen breakage syndrome**

Beta-galactosidase-1 deficiency *see* **Gm1 gangliosidosis**

Beta thalassemia

Definition

Beta thalassemia is an inherited disorder that affects the beta globin (protein molecules) chains. These chains are required for the synthesis of hemoglobin A (a compound in the blood that carries oxygen to the cells and carbon dioxide away from the cells). A decrease of beta globin chains causes early destruction of the red blood cells. There are four types of the disorder and they range in severity of symptoms.

The thalassemias were first discovered by Thomas Cooley and Pearl Lee in 1975. Early cases of the disease were reported in children of Mediterranean descent and therefore the disease was named after the Greek word for sea, *thalasa*.

Description

Beta thalassemia results due to a defect in the beta globin **gene**. Shortly after birth, the body converts from producing gamma globin chains, which pair with alpha globin chains to produce fetal hemoglobin (HbF), to producing beta globin chains. Beta globin chains pair with alpha globin chains to produce adult hemoglobin (HbA). Due to the decreased amount of beta globin chains in individuals with beta thalassemia, there is an excess of free alpha globin chains. The free alpha globin chains become abnormal components in maturing red blood cells. This leads to destruction of the red blood cells by the spleen and a decreased number of red blood cells in the body. Individuals with beta thalassemia may continue producing gamma globin chains in an effort to increase the amount of HbF and compensate for the deficiency of HbA.

There are four types of beta thalassemias. These include beta thalassemia minima, minor, intermedia, and major. Beta thalassemia minima and beta thalassemia minor are less severe and usually asymptomatic. Beta thalassemia minima is known as the silent form of the disorder. There are no major hematologic (blood and blood forming tissue) abnormalities. The only noted abnormality is the decrease in beta globin production. Beta thalassemia minor is rare. A person with this type of the disorder inherits only one beta globin gene. Although children are usually asymptomatic, they do have abnormal hematologic (blood) findings.

Beta thalassemia intermedia and major often require medical treatment. Beta thalassemia intermedia is frequently found during the toddler or preschool years. It is considered to be the mild form of thalassemia major and usually does not require blood transfusions. Thalassemia major is typically diagnosed during the first year of life. There are two designations for beta thalassemia major, beta zero and beta positive. In type beta zero there is no adult hemoglobin (HbA) present due to the very small production of beta globin. In type beta positive there is a small amount of HbA detectable. In both forms of beta thalassemia major, individuals will experience severe fatigue due to the decrease or absence of adult hemoglobin (HbA), which is needed to carry oxygen to the cells, and is necessary for cellular survival.

Alternate names associated with beta thalassemia minor include thalassemia minor, minor hereditary leptocyosis, and heterozygous beta thalassemia. Alternate names associated with beta thalassemia intermedia include intermedia Cooley's anemia and thalassemia intermedia. Alternate names associated with beta thalassemia major include Cooley's anemia, erythroblastoic anemia of childhood hemoglobin lepore syndrome, major hereditary leptocytosis, Mediterranean anemia, mocrocythemia, target cell anemia, and thalassemia major.

Genetic profile

Beta thalassemia is an autosomal recessive disorder. A person who is a carrier will not develop the disorder but may pass the gene for the disorder onto their child. There is a 25% chance for each pregnancy that the disorder will be passed onto the children if both parents are carriers for the trait and a 100% chance if both parents have the trait.

Individuals with thalassemia minor are carriers for the beta globin gene and therefore possess only one of the genes necessary to express the disorder. These individuals are usually asymptomatic or have very few symptoms. Individuals with thalassemia major express both abnormal genes for beta globin and therefore will have the disease. These individuals show severe symptoms for the disorder.

The beta globin gene is found on chromosome 11. Mutations (inappropriate sequence of nucleotides, the building blocks of genes) resulting in beta thalassemia are usually caused by substitutions (switching one nucleotide for another) although some may be caused by deletions (part of a chromosome, a structure that places genes in order, is missing). Substitutions occur within the nucleotide and deletions occur on the chromosome that the beta globin gene is found on.

Demographics

Beta thalassemia affects males and females equally. It commonly occurs in people of Mediterranean heritage. It is also found in families descending from Africa, the Middle East, India, and Southeastern Asia.

Signs and symptoms

Symptoms for beta thalassemia vary in severity based on the type of the disorder.

Beta thalassemia minima

There are no symptoms for this type. It is considered to be a "silent" form of beta thalassemia.

Beta thalassemia minor

Individuals with this type of beta thalassemia may be asymptomatic or experience very few symptoms. Symptoms may be worse in individuals that are pregnant, under stress, or malnourished. Symptoms may include:

- Fatigue. This may be the only symptom that an individual with beta thalassemia minor exhibits. Fatigue is caused by the decreased oxygen carrying capacity of the red blood cells, resulting in lowered oxygenation for cells and tissues.
- Anemia. Anemia is a decrease in the amount of hemoglobin in the blood. Hemoglobin is needed to carry oxygen on the red blood cells. In beta thalassemia minor there is a decrease in adult hemoglobin (HbA) and an increase in hemoglobin A2. Hemoglobin A2 is a minor hemoglobin that contains delta globin chains in the place of beta globin chains. Anemia is most likely to occur during pregnancy.
- Splenomegaly. Enlargement of the spleen may occur due to increased removal of defective red blood cells. This is rarely seen in individuals with beta thalassemia minor and may be accompanied by pain in the upper left portion of the abdomen.
- Skin. The skin color of individuals with beta thalassemia minor may be pale (pallor) due to oxygen deprivation in blood.

Beta thalassemia intermedia

Individuals with this form of beta thalassemia usually begin to show symptoms during toddler or preschool years. These individuals present with many of the same symptoms as beta thalassemia major, however, symptoms for beta thalassemia intermedia are less severe and may include:

- Anemia. In individuals with beta thalssemia intermedia, hemoglobin levels are greater than 7g/dl but they are less than normal. Normal levels for hemoglobin are 13-18 for males and 12-16 for females.
- Hyperbilirubinemia. Bilirubin is a yellow pigment of bile that is formed by the breakdown of hemoglobin in the red blood cells. Excess amounts of bilirubin in the blood is caused by the increased destruction of red blood cells (hemolysis) by the spleen.
- Splenomegaly. Enlargement of the spleen is caused by increased removal of defective red blood cells. Red blood cells are defective due to the increased amount of inclusion bodies caused by circulation of free alpha globin chains.
- Hepatomegaly. Enlargement of the liver may be caused by a build-up of bile due to increased amounts of bilirubin in the blood.
- Additional abnormalities. Individuals with beta thalassemia intermedia may have a yellow discoloration (jaundice) of the skin, eyes, and mucous membranes caused by increased amounts of bilirubin in the blood. Individuals may also suffer from delayed growth and abnormal facial appearance.

Beta thalassemia major

Individuals with this form of beta thalassemia present with symptoms during the first year after birth. Symptoms are severe and may include:

- Severe anemia. Individuals with beta thalassemia major suffer from a hemoglobin level of less than 7 mg/dl.
- Hyperbilirubinemia. Individuals will have an increased amount of bilirubin in the blood. This is due to the increased destruction of red blood cells (hemolysis) by the spleen.
- Jaundice. Individuals may experience a yellow discoloration of the skin, eyes, and mucous membranes caused by increased amounts of bilirubin in the blood.
- Extramedullary hematopoiesis. Abnormal formation of red blood cells outside of the bone marrow may occur in the body's attempt to compensate for decreased production of mature red blood cells. This can cause masses or the enlargement of organs, which may be felt during physical examination.
- Splenomegaly. Enlargement of the spleen may result due to increased destruction of red blood cells and the occurrence of extramedullary hematopoiesis.
- Hepatomegaly. Enlargement of the liver may result due to accumulation of bile or the occurrence of extramedullary hematopoiesis.
- Cholithiasis. This is the presence of stones in the gallbladder, which may lead to blockage and cause bile to be pushed back into the liver.
- Bone marrow expansion. The bone marrow becomes expanded due to the increase of the production of red blood cells (erythropoiesis) in an attempt to produce more mature red blood cells and decrease the anemic state of the body.
- Facial changes. Due to expansion of the bone marrow, children will develop prominent cheekbones, depression of the nasal bridge, and protrusion of the upper jaw. These facial changes are a classic sign in children with untreated beta thalassemia.
- Iron overload. Iron overload of the tissues can be fatal and is due to erythroid (red blood cell) expansion. The increased destruction of a vast amount of red blood cells causes increased amounts of iron to be released from the hemoglobin.
- Cardiovascular abnormalities. Accumulation of iron deposits in the heart muscle can lead to cardiac abnormalities and possibly cardiac failure.
- Additional abnormalities. Individuals may also suffer from pale skin, fatigue, poor feeding, failure to thrive, and decreased growth and development.

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Globin—One of the component protein molecules found in hemoglobin. Normal adult hemoglobin has a pair each of alpha-globin and beta-globin molecules.

Hemoglobin—Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hepatomegaly—An abnormally large liver.

Splenomegaly—Enlargement of the spleen.

Diagnosis

Completing a family history, performing a complete physical examination, and results of blood (hematological) tests can lead to a diagnosis of beta thalassemia. Bone abnormalities and masses or enlarged organs may be recognized during physical examination. Prenatal testing to detect beta thalassemia can be done by completing an **amniocentesis** (obtaining a sample of amniotic fluid, which surrounds the fetus during pregnancy). Lab results will vary depending on the type of beta thalassemia that an individual presents with.

Normal hemoglobin results are 13–18 g/dl for males and 12–16 g/dl for women. Normal red blood cell counts are 4.7–6.1 million for males and 4.2–5.4 million for females. In individuals with beta zero form of beta thalassemia major, there will be no HbA present in the blood.

Symptoms of beta thalassemia minor may be similar to those of sideroblastic anemia (a disorder characterized by low levels of hemoglobin, fatigue, and weakness) and sickle cell disease (a disease that changes red blood cell shape, rendering it incapable of functioning).

Symptoms of beta thalassemia major may be similar to those of hereditary spheocytic hemolytic anemia (presence of sphere shaped red blood cells).

Treatment and management

Beta thalassemia minima and minor usually require no treatment. Pregnant women that suffer from beta thalassemia minor may require blood transfusions to keep hemoglobin levels normal. Individuals with beta thalassemia intermedia and major can be treated with blood transfusions and iron chelation (binding and isolation of metal) therapy. Although individuals with beta thalassemia intermedia do not usually require transfusions, in certain cases it may be necessary.

Blood transfusions are performed in individuals that present with severe symptoms such as anemia and impaired growth and development. Children may receive transfusions every four to six weeks. A high risk associated with transfusions is iron overload, which is fatal. Iron overload results due to inadequate amounts of serum transferring (a molecule that exchanges iron between body tissues), which is needed to bind and detoxify iron. Iron accumulation can lead to dysfunction of the heart, liver, and endocrine glands.

Monitoring iron levels in the body is essential. Individuals receiving blood transfusions should keep total body iron levels at 3–7 mg of iron per gram of body weight. As of 2000, there are three methods of measuring iron levels in the body. These include a serum ferritin test, liver biopsy, and radiological study performed by the Superconducting Quantum Interference Device (SQUID).

The serum ferritin (iron storage protein) test is completed by testing a blood sample for ferritin content. This method is the easiest and most affordable way of testing for body content of iron, but it is not reliable. A liver biopsy is an invasive procedure that requires removal of a small piece of the liver. Studies have shown that a liver biopsy is very accurate in measuring the level of iron stores in the body. The third method, which requires a Superconducting Quantum Interference Device, is also very accurate in measuring iron stores. The SQUID is a highly specialized machine and few centers in the world possess this advanced technology.

Iron overload can be prevented with the use of iron chelating therapy. Chelating agents attract the excess iron and assist with the process of binding and detoxifying this iron in the body. The drug deferoxamine (desferol) is one of the most widely used iron chelating agents. Treatment is completed through nightly infusions of deferoxamine by a pump or with daily intramuscular injections. Infusion by pump is used for the administration of high doses and low doses are given through injections. Iron chelation therapy by oral administration with a drug named deferiprone has been under experimental study and may be an alternative to deferoxamine.

Individuals receiving blood transfusions should pay close attention to iron intake in the diet. It is recom-

mended that children under age 10 keep dietary iron intake at 10 mg/day or less. Individuals age 11 or older should keep dietary iron intake at 18 mg/day or less. Foods high in iron include: beef, beans, liver, pork, peanut butter, infant cereal, cream of wheat, prunes, spinach, raisins, and leafy green vegetables. Individuals should read food labels and avoid using cast iron cookware, which can provide more iron in food during cooking.

Increased amounts of iron in the body can cause a decrease in calcium levels that can impair organs which aid in building strong bones. Individuals with beta thalassemia major are at risk for developing osteoporosis (disease resulting in weakened bones). Increased dietary intake of calcium and vitamin D can help increase the storage of calcium in the bones, thus making the bones stronger and decreasing the risk for osteoporosis.

Bone marrow transplantation is another form of treatment for beta thalassemia. Outcomes of transplantation are greatly influenced by the health of the individual. This form of treatment is only possible if the individual has a suitable donor.

Researchers are investigating the use of the drugs hydroxyurea and butyrate compounds to increase the amounts of fetal and total hemoglobin in individuals with beta thalassemia. Studies using **gene therapy**, such a stem cell replacement, are also being conducted.

Social and lifestyle issues

Children with beta thalassemia major that is not diagnosed and treated early may develop changes in the bone structure of the face due to the expansion of bone marrow. Supportive counseling may benefit children who feel inadequate or refuse to participate in social activities due to their appearance.

Adolescents may require counseling concerning the effects that blood transfusions and iron chelation therapy may have on their social lifestyle.

Parents may need to seek counseling or attend support groups that focus on the time demand and lifestyle changes of caring for a child diagnosed with beta thalassemia.

Prognosis

Prognosis for beta thalassemia is good for individuals diagnosed early and those who receive proper treatment. Children with beta thalassemia major live 20-30 years longer with treatment by blood transfusions and iron chelation therapy.

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Cooley's Anemia Foundation, Inc. 129-09 26th Ave. #203, Flushing, NY 11354. (800) 522-7222 or (718) 321-2873. <http://www.thalassemia.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Heart, Lung, and Blood Institute. PO Box 30105, Bethseda, MD 20824-0105. (301) 592-8573. nhlbiinfo@rover.nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Laith F. Gulli, MD
Tanya Bivens, BS

Bicuspid aortic valve

Definition

Bicuspid aortic valve is the most common malformation of the heart valves. In this type of deformity, the aortic valve has only two cusps, which are rigid points

such as that seen on leaves, instead of the three cusps normally present. This condition may lead to abnormalities in the flow of blood from the heart to the aorta, leading to changes in the function of the heart and lungs. Treatment consists of surgical repair or replacement of the valve.

Description

A valve is a device that allows a fluid to flow in only one direction in a defined path, thereby preventing backflow of the fluid. The heart has four such valves, which allow the blood to flow in an orderly pattern through each of the four chambers of the heart and out into the largest artery of the body, the aorta. The aorta, in turn, branches into other blood vessels in the neck, limbs, and organs of the body to supply it with oxygenated blood.

The aortic valve divides the left ventricle of the heart and the aorta. It is the last valve before blood leaves the heart and passes into the aorta. The valve is formed during pregnancy and is normally composed of three separate cusps or leaflets, which, when closed, form a tightly sealed barrier that prevents backflow of blood from the aorta into the heart. Thus, when the heart contracts or pumps, the aortic valve opens and allows blood to pass from the heart into the aorta, and when the heart relaxes, the aortic valve closes and prevents backflow of blood from the aorta into the heart.

The three-cusp structure of the valve is essential for its proper function, and was noted as far back as the fifteenth century when the great master of the High Renaissance, Leonardo da Vinci, reported on his observations of anatomy and blood circulation. In bicuspid aortic valve, the aortic valve fails to form properly during development in the womb; for reasons that are unclear, two of the three cusps fail to separate properly and remain attached along one edge, resulting in an aortic valve with only two cusps.

The bicuspid aortic valve is the most common heart valve defect at birth, and many people live a normal life without even being aware of this condition. Unfortunately, bicuspid aortic valves are also more prone to disease than the normal three cusped valves. Over the years, conditions such as restricted blood flow to the aorta (aortic stenosis), backflow of blood from the aorta into the heart (aortic regurgitation, or aortic insufficiency) and valve infection (endocarditis) are often detected with associated symptoms during the adult years as progressive damage is done to the bicuspid aortic valve.

Other conditions that may occur with bicuspid aortic valve include aneurysm of the aorta (ballooning out of the aorta wall), and aortic dissection (a life-threatening split in the layers of the aorta).

Genetic profile

Most occurrences of bicuspid aortic valve appear to be sporadic (i.e., random, and not associated with a inherited defect) and are not passed on from parent to child. However, there have been some reports that the valve malformation appears in multiple members of the same family. In at least one report, this familial occurrence appears to be inherited in an autosomal dominant pattern with reduced penetrance (not showing the malformation, despite possessing the genetic cause for it). However, if there is some sort of genetic or inherited cause in some patients with bicuspid aortic valve, it has not been identified. For purposes of **genetic counseling**, bicuspid aortic valve can be regarded as a sporadic condition with an extremely low risk of being transmitted from parent to child.

Demographics

Bicuspid aortic valve has been reported to occur in 1-2% of the general population, and is the most common valve defect diagnosed in the adult population, accounting for up to half of the operated cases of aortic stenosis. For reasons that are unclear, bicuspid aortic valve is three to four times more likely in males than in females, though some researchers suggest that the condition may simply be diagnosed more in males because of the higher rates of calcium deposits in men that bring the aortic valve to medical attention.

Interestingly, bicuspid aortic valve is also found with other conditions, including the genetic disorder Turner's syndrome, or in patients with a malformation called coarctation of the aorta (narrowing of the aorta). It has been reported that approximately 35% of patients with Turner's syndrome and up to 80% of patients with coarctation of the aorta have an associated bicuspid aortic valve. The significance of these associations is unclear.

Signs and symptoms

Many people with bicuspid aortic valve experience no symptoms, and may live their entire lives unaware of the condition. However, progressive damage or infection of the valve may lead to three serious conditions: aortic stenosis, aortic regurgitation, or endocarditis.

As a person ages, calcium deposits on a bicuspid aortic valve making it stiff. Eventually, the valve may become so stiff that it does not open properly, making it more difficult for blood to leave the heart and pass into the aorta and resulting in aortic stenosis. When this blockage becomes serious enough, people may experience shortness of breath, chest pain, or fainting spells. These symptoms usually begin between the ages of 50

and 60 years old. Eventually, the blockage can become so bad that blood backs up in the heart and lungs instead of going out to supply the rest of the body with oxygen (congestive heart failure). Additionally, this condition can lead to thickening of the heart wall, which may cause abnormal heart rhythms leading to sudden death.

Aortic regurgitation results when the valve fails to close properly. People who develop this condition may become short of breath when exerting themselves. The extent of symptoms experienced by the patient depends on the severity of the aortic regurgitation.

Finally, bacteria may deposit on the malformed bicuspid aortic valve, causing endocarditis. People with endocarditis may have symptoms of lingering fevers, fatigue, weight loss, and sometimes damage to the kidneys or spots on their fingers and hands.

Other dangerous conditions associated with bicuspid aortic valve include aortic aneurysm and aortic dissection. People with aortic aneurysms usually do not experience symptoms unless the aneurysm ruptures, but people with aortic dissection experience tearing back pain. Aortic aneurysm rupture and aortic dissection are very dangerous and can rapidly lead to death if not promptly treated.

Diagnosis

Any of the symptoms of aortic stenosis, aortic regurgitation, or endocarditis should prompt a search for an underlying malformation of the aortic valve. Aortic stenosis or regurgitation is diagnosed by a combination of physical exam, cardiovascular tests and imaging. The earliest sign of aortic valve problems is a murmur (the sound of abnormal patterns of blood flow) heard with a stethoscope. When the valve has high levels of calcium deposits, a characteristic clicking sound can also be heard with the stethoscope just as the stiff valve attempts to open. Later signs include a large heart seen on x ray or by a special electrical test of the heart, called an ECG or EKG (electrocardiogram).

If these signs are present, it suggests that the aortic valve may be damaged. The next test to be performed is echocardiography, a method that uses ultrasound waves to look at the aortic valve, similar to the way in which ultrasound is used to look at a fetus during pregnancy. Often, only two cusps are seen on the aortic valve during the echocardiography, confirming a diagnosis of bicuspid aortic valve.

Endocarditis is diagnosed by demonstrating the presence of bacteria in the blood stream. This is performed by taking blood from the patient and growing the bacteria on plates with specialized nutrients. Skilled technicians can then use different tests to identify which species of bacteria is present so that appropriate treatment can be started. The diagnosis of endocarditis is also confirmed by using echocardiography to look for bacterial growths on the aortic valve. During the echocardiography, a bicuspid valve is often seen and explains the tendency to develop endocarditis.

KEY TERMS

Aorta—The main artery located above the heart which pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

Aortic regurgitation—A condition in which the aortic valve does not close tightly, allowing blood to flow backwards from the aorta into the heart.

Aortic stenosis—A condition in which the aortic valve does not open properly, making it difficult for blood to leave the heart.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Coarctation—A narrowing of the aorta that is often associated with bicuspid aortic valve.

Echocardiogram—A non-invasive technique, using ultrasonic waves, used to look at the various structures and function of the heart.

Electrocardiogram (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Endocarditis—A dangerous infection of the heart valves caused by certain bacteria.

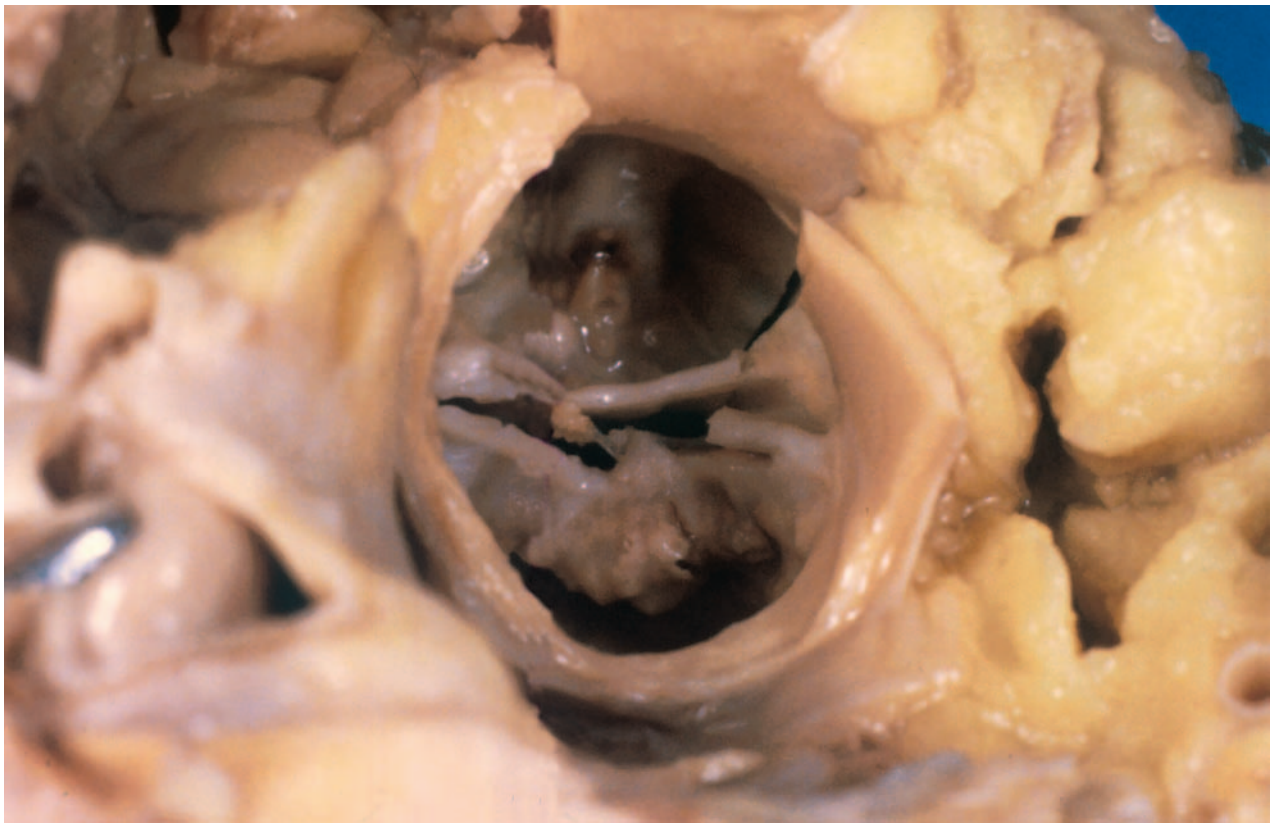
Heart valve—One of four structures found within the heart that prevents backwards flow of blood into the previous chamber.

Murmur—A noise, heard with the aid of a stethoscope, made by abnormal patterns of blood flow within the heart or blood vessels.

Reduced penetrance—Failing to display a trait or disease despite possessing the dominant gene that determines it.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Stethoscope—An instrument used for listening to sounds within the body, such as those in the heart or lungs.



This view of a human heart specimen clearly shows the structure of a bicuspid aortic valve. *(Custom Medical Stock Photo, Inc.)*

Treatment and management

Most people with bicuspid aortic valve will not experience any complications or symptoms and will not require treatment. However, in patients with any complication of valve damage, as previously discussed, treatment may be necessary.

In younger patients who have aortic stenosis, a procedure can be performed in which a small balloon is inserted through one of the major blood vessels and into the aortic valve. The balloon is then inflated, creating a bigger opening for blood to pass. Alternatively, an "open heart" procedure can be performed to cut the valve into a more normal configuration. These treatments are usually temporary, and later in life the patient, as well as any adult with advanced aortic stenosis, will most likely require aortic valve replacement.

Valve replacement is an "open heart" operation where the original malformed valve is removed and replaced with a new valve. This new valve can come from a human donor who has died, or from cows or pigs, or even from another part of the patient's heart. These valves function well, but may need to be replaced after 10 to 20 years, as they wear out. Another option is to use an artificial valve made of metal, plastic, or cloth. However, people who receive these artificial valves need to take blood thinners every day in order to prevent blood clots from forming on the new valve.

Patients with endocarditis need to be hospitalized and treated with high does of antibiotics given through a vein for several weeks. Damage done to the valve by the bacteria may make it necessary for a valve replacement procedure to be performed after the patient has recovered from the infection.

In any case, people who have been identified as having bicuspid aortic valve should be followed regularly by a cardiologist, with possible consultation with a cardiothoracic surgeon. The function of the bicuspid aortic valve should be followed through the use of echocardiography, and the state of the heart itself should be followed by regular electrocardiograms.

It should be noted that children with aortic stenosis may not be able to engage in vigorous physical activity without the risk of cardiac arrest and should consult their physician. In addition, all people with bicuspid aortic valve should receive antibiotics prior to any dental procedure or surgery; these procedures may allow bacteria to enter the blood stream and could result in endocarditis if antibiotics are not given beforehand.

Prognosis

Most people born with bicuspid aortic valve experience no symptoms or complications, and their lives do not differ from someone born with a normal aortic valve. In patients who do experience complications and require valve replacement, risks of the operation generally depend on age, general health, specific medical conditions, and heart function. It is better to perform the operation before any of the advanced symptoms (shortness of breath, chest pain, fainting spells) develop; in patients without advanced symptoms, the risk of a bad outcome of surgery is only 4%. If a person with advanced symptoms chooses not to undergo surgery, the risk of death within three years is more than 50%. In general, valve replacement greatly reduces the amount and severity of symptoms and allows the patient to return to their normal daily activities without discomfort after they recover from the surgery.

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American Heart Association. 7272 Greenville Ave., Dallas, TX 75231-4596. (214) 373-6300 or (800) 242-8721. inquire@heart.org. <http://www.americanheart.org>.

Congenital Heart Anomalies Support, Education, and Resources. 2112 North Wilkins Rd., Swanton, OH 43558. (419) 825-5575. <http://www.csun.edu/~hfmth006/chaser>.

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Oren Traub, MD, PhD

Biotinidase deficiency

Definition

Biotinidase deficiency is a rare inherited defect in the body's ability to use dietary biotin, one of the B vitamins. The disease is also known as juvenile or late-onset multiple carboxylase deficiency.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Co-enzyme—A small molecule such as a vitamin that works together with an enzyme to direct a biochemical reaction within the body.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

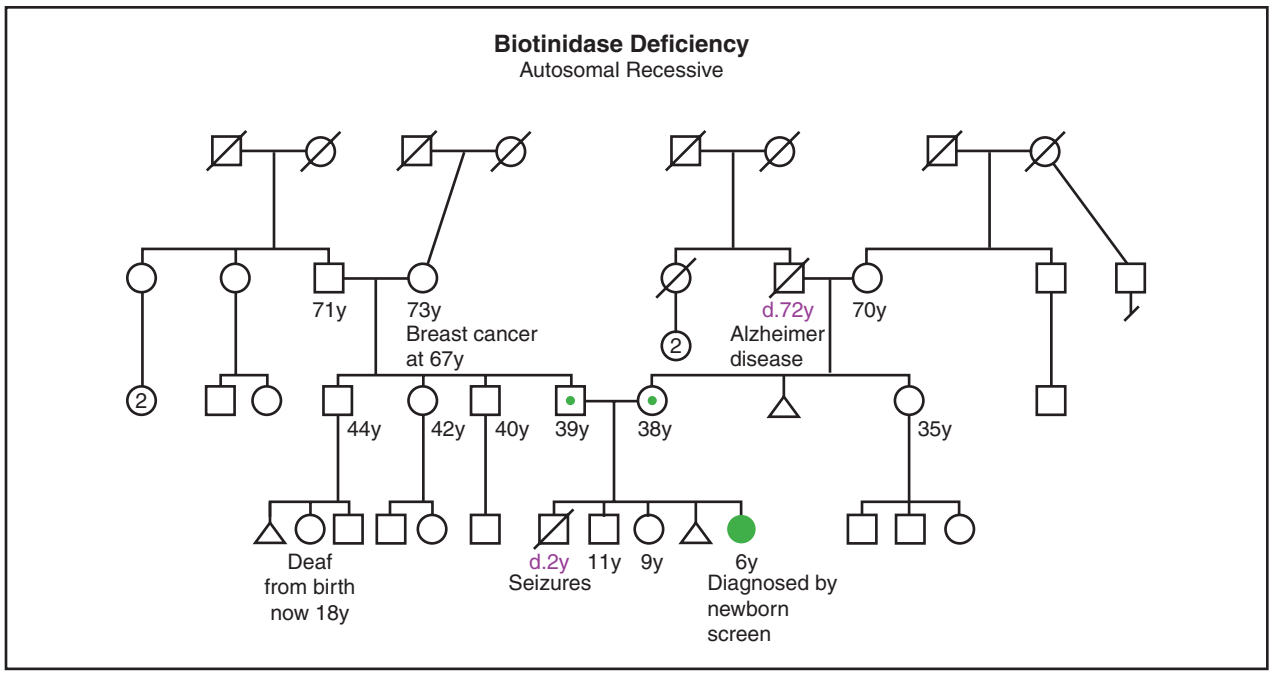
Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Description

Biotin is essential as a co-factor (co-enzyme) for the reactions of four enzymes called carboxylases. These enzymes, in turn, play important roles in the metabolism of sugars, fats, and proteins within the human body. Another key enzyme, biotinidase, recycles biotin from these reactions so it can be used again. A defect in the biotinidase **gene** results in decreased amounts of normal enzyme, thus preventing the reuse of biotin. In turn, this leads to a disruption of the function of the four carboxylases that depend on biotin, and results in a variety of abnormalities of the nervous system and skin. Since



(Gale Group)

symptoms usually do not appear immediately at birth, biotinidase deficiency is also referred to as late-onset or juvenile multiple carboxylase deficiency. A related disorder, early-onset or neonatal multiple carboxylase deficiency, is caused by the lack of a different enzyme, holocarboxylase synthetase, and, as the name suggests, results in symptoms in the newborn period.

Genetic profile

Inheritance pattern

Biotinidase deficiency is an autosomal recessive disorder affecting both males and females. In individuals with this disorder, both copies of the biotinidase gene are defective. Both parents of an affected child have one abnormal copy of the gene, but usually do not show symptoms because they also have one normal copy. The normal copy provides approximately 50% of the usual enzyme activity, a level adequate for the body's needs. Individuals with one abnormal copy of the gene and 50% enzyme activity are said to be carriers or heterozygotes. As is typical of autosomal recessive **inheritance**, their risk for having another child with the disorder is 25% in each subsequent pregnancy.

Gene location

The gene for biotinidase is located on the short arm of chromosome 3 (3p25). As of 1999, at least 40 different mutations in this gene had been identified in individuals with biotinidase deficiency. The fact that there are a number of different types of mutations helps explain why symptoms are variable from one individual to another. However, the presence of variability even within a family suggests there may be other, as yet unknown, factors that affect the severity of the disease.

Demographics

Individuals with biotinidase deficiency have been described in various ethnic groups worldwide. In the general population, the incidence of the disease is estimated at about one in 60,000 individuals and one in every 123 individuals is a carrier.

Signs and symptoms

The onset of symptoms is typically between three and six months of age but varies widely from one week to several years. The most common clinical features are hair loss (alopecia), skin rash (dermatitis), seizures (convulsions), decreased muscle tone (hypotonia), difficulty walking (ataxia), breathing problems, redness of the eyes (conjunctivitis), hearing and vision loss, and developmental delay. Children with biotinidase deficiency are prone to fungal and bacterial infections, suggesting that

the immune system is also affected. Symptoms are highly variable among affected individuals even, within a single family.

Biotinidase deficiency is classified as either partial or profound. If there is at least 10% enzyme activity, the deficiency is considered partial and is usually associated with minimal to mild symptoms. Profound biotinidase deficiency, defined as less than 10% of normal activity, is characterized by many of the symptoms mentioned above, and can, if left untreated, result in coma and death.

Diagnosis

Children with profound biotinidase deficiency may show general signs such as vomiting, seizures, and low muscle tone, all of which can be associated with a number of different disorders. Diagnosis can be difficult because of the many different enzyme deficiencies (inborn errors of metabolism) with similar symptoms and test results. For example, abnormally high amounts of certain acidic products in the blood and urine can be typical of a number of different metabolic disorders including biotinidase deficiency. Accurate diagnosis is made by measuring the activity of the enzyme in blood or skin cells. A number of states and countries test for this disorder at birth as part of a comprehensive newborn screening program. Infants whose tests indicate they have biotinidase deficiency can be started on treatment before symptoms appear. With regular treatment these infants usually remain symptom-free.

Carrier testing

Most carriers can be detected by measuring biotinidase activity in their blood. Fifty percent of normal enzyme activity is characteristic of carriers. Specific DNA tests can usually detect the particular gene mutation in any affected individual or carrier.

Prenatal diagnosis

If a couple has had one child with biotinidase deficiency, they can be offered prenatal testing in future pregnancies. Prenatal testing is accomplished by measuring biotinidase activity in amniotic fluid cells obtained by **amniocentesis** around the sixteenth week of pregnancy. Alternatively, if specific gene mutations have been identified in the parents, fetal DNA from amniotic fluid cells can be studied to test for these same mutations in the fetus. Carrier couples who are considering prenatal diagnosis should discuss the risks and benefits of this type of testing with a geneticist or genetic counselor.

Treatment and management

Treatment of the profound form of biotinidase deficiency consists of giving large doses of biotin orally. Partial deficiencies are usually treated with lower doses. The biotin must be in a free form; that is, not attached to other molecules as would be the case with the biotin found in food. Properly treated, biotinidase deficiency is not a life-threatening condition, but biotin treatment must continue throughout life. No treatment is needed before birth because the developing fetus is provided with sufficient free biotin from the mother.

Prognosis

Daily treatment with free biotin usually results in rapid improvement of the skin condition, hair regrowth, and a lessening or cessation of seizure activity. Many children whose development has been affected by biotinidase deficiency have shown some improvement after treatment. Hearing and vision losses are less reversible. Children who are diagnosed at birth through newborn screening programs rarely develop symptoms if they are started on biotin replacement therapy immediately.

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Sallie Boineau Freeman, PhD

Bipolar disorder

Definition

Bipolar disorder is characterized by mood swings, which are unpredictable and range from mania (elevated and irritable mood) to **depression** (a mood characterized by loss of interest and sadness). The disorder causes significant difficulties or impairment in social, occupational, and general functioning capabilities.

Description

Bipolar Type II (BT II) disorder is a psychological disorder characterized by fluctuation of cycles (time periods) of mania and depression. The manic cycle or phase is commonly associated with irritability, decreased need for sleep (sleep disruption), euphoria (an exaggerated false self-perception of feeling good), social extroversion (excessive friendliness), and feeling more important than one truly is (grandiosity). The depressive episode or cycle is correlated with a broad spectrum of symptoms. Most patients in depressive cycles exhibit common symptoms, which include fatigue, impaired concentration/decision making, and altered sleep and appetite patterns. This cycle can further progress to the level where patients feel excessively shameful and guilty. In totality, the symptoms for the depressive cycle can lead to thoughts of death or dying. The disorder is also called Manic-Depressive Psychosis, and Major Affective Disorder.

Genetic profile

There is significant evidence that correlates BT II with genetic causes. Studies have shown monozygotic twins (identical twins) have an 80% concordance rate (presence of the same disorder in twins). Additionally, studies have demonstrated that the disorder is transmitted to children (progeny) by autosomal dominant **inheritance**. This means that either affected parent has a 50% chance of having a child (regardless if the child is male or female) with the disorder.

Further studies concerning the genetic correlations have revealed specific **chromosomes** (the structure that contains genes) that contain mutated genes. Susceptible genes are located in specific regions of chromosomes 13, 18, and 21. The building blocks of genes, called nucleotides, are normally arranged in a specific order and quantity. If these nucleotides are repeated in a redundant fashion a genetic abnormality usually results. Recent evidence suggests a special type of nucleotide sequence (CAG/CTG repeats) is observed in patients with BT II on chromosome 18. However, the presence of this sequence does not worsen the disorder or change the age of onset. It is currently thought that expression of BT II involves multiple mutated genes. Further research is ongoing to determine precise mechanisms and to develop genetic markers (gene tags) for predicting which individuals are at higher risk.

Demographics

Manic-depression is a common psychological disorder that is difficult to diagnose (detect). It is estimated that about three million people in the United States are affected. Community oriented studies suggest that the lifetime prevalence (number of cases in terms of time) is approximately 0.5%. The disorder is more common in women than in men. Women have been observed at increased risk of developing subsequent episodes in the immediate period after giving birth. After treatment, most patients with BT II return to fully functional levels. Approximately 15% of patients do not display functioning due to persistent mood changes, which continues to cause occupation and interpersonal difficulties.

Signs and symptoms

The following signs and symptoms are indicative of bipolar disorder:

1. Presence or history of major depressive episodes:
   - Feeling sad or empty
   - Decreased interest in pleasure and daily activities
   - Weight changes (gain or loss)
   - Sleep changes (difficulty falling asleep or waking up)
   - Thinking and moving in an agitated or slowed manner
   - Feeling loss of energy or fatigued for most of the day
   - Feeling worthless or having unnecessary guilt for nearly every day
   - Decreased ability to think, concentrate, or indecisiveness nearly every day
   - Recurrent thoughts of death or suicide (without a plan or attempts)
2. Presence or history of at least one hypomaniac episode (persistent elevated or irritable mood lasting throughout at least four days). The criteria includes three or more of the following:
   - Grandiosity
   - Decreased requirement for sleep (patient feels rested after only three hours of sleep)

- Pressure or overly talkative
- Racing thoughts (flight of ideas)
- Irrelevant distractibility (attention). The patient is easily distracted to something that is unimportant.
- Increase in goal-directed activities
- Excessive involvement with risky pleasurable activities (sexual indiscretions, buying sprees, or foolish monetary investments)

3. There is an uncharacteristic change in functioning
4. Mood and functioning changes are detected by others
5. Lacks severity since impairment is not pronounced
6. There has never been a manic or mixed episode. A mixed episode is characterized by a period of time, usually about one week in which the patient exhibits diagnostic criteria for both major depressive and manic episodes nearly every day. The criteria for manic and hypomanic episodes are identical.
7. The symptoms are severe to cause problems in occupation, social, and relationship functioning.
8. The symptoms are not associated with another medical condition, which can present with criteria similar to a manic episode.

For BT II to be chronic, criteria for the depressive episode should be met continuously for at least two years. Patients with concurrent catatonic features also exhibit disturbances with movement (immobility, peculiar or excessive motor activity). The features of BT II with melancholia often include near complete absence of the capacity for pleasure. Patients with BT II and atypical features usually present with mood reactivity (mood improves with positive event) and two or more of the following: increased appetite or significant weight gain; difficulty waking up from sleep; heavy, almost paralyzed feeling in the arms or legs; long term sensitivity to interpersonal rejection. BT II with postpartum onset usually occurs within four weeks after childbirth. Manic-depression with a seasonal pattern is also related to seasonal change, age, gender, and latitude. The prevalence of the seasonal specifier increases with higher latitudes, young persons, winter months, and female gender. Rapid cycler's are those who exhibit the criteria for BT II and have at least four episodes of a mood disturbance in the previous 12 months.

Diagnosis

The diagnosis of BT II is based on the specific criteria described in the *Signs and Symptoms* section. BT II should be distinguished from Unipolar (major) depression. Patients who exhibit BT II often present with signs of eating more (hyperphagia), sleeping more (hypersomnia), very low energy levels, overweight, and worsening of mood during evening hours. The BT II affected person also tends to deny or minimize poor judgement and acting differently when compared to others. Close friends, family members, and roommates are often very helpful in assisting the clinician make the correct diagnosis. Unipolar (major) depression usually presents with anxiety, difficulty sleeping, and loss of appetite, loss of weight and feeling worse during morning hours, which improves as the day goes on.

KEY TERMS

Nucleotides—Building blocks of genes, which are arranged in specific order and quantity.

Complications

Suicide is the major complication of BT II. This is related to time. The longer the depression the more serious a threat, especially when there are secondary reinforcements, which promote such aggression. Alcoholics and patients with chronic (long-term) medical diseases are particularly prone to planning and implementing a suicide attempt. There are four major groups that are likely to carry out a suicide attempt. They include:

- Individuals who are overwhelmed by problems in living. They tend to be acts related to aggression and impulsive behaviors, not significant depressive episodes.
- Individuals who are attempting to control others.
- High-risk groups who are chronically ill with another medical disease.
- Patients with other severe types of psychotic illness, delusions, and paranoia.

Treatment and management

Treatment of BT II is focused along three categories: standard medications, psychosocial interventions, and newly discovered medications (gabapentin augmentation).

Standard medications

Standard treatments include medications such as lithium carbonate and sodium valproate. With lithium carbonate, beneficial effects usually appear one to two weeks after administration with oral doses. The response rate with lithium is encouraging since 70-80% of patients with acute manic attacks show improvement of symptoms. Side effects from lithium treatment include gas-

trointestinal discomfort, diarrhea, baldness, skin eruptions, and fluid retention. Lithium is primarily useful as a prophylactic (prevention) medication from future attacks. Another medication, haloperidol can be given initially and gradually reduced for lithium replacement and maintenance.

Valproic acid is a second line medication intended for patients who respond poorly to or cannot tolerate side effects. Valproic acid seems to be more efficient than lithium for treating BT II patients with the rapid cycling variety (more than four episodes a year).

Recent reports indicate a new medication, gabapentin (an anti-manic medication), is efficient for treating acute phase (sudden onset) BT II. This chemical seems to be particularly useful when combined with other psychotropics (medications commonly used to treat mental illnesses). Very recent evidence suggests that gabapentin can potentially induce aggressive and disruptive behavior in children treated with this drug for seizures (abrupt and abnormal jerking of muscles due to abnormal firing of nerve impulses from the brain).

Psychosocial interventions

Psychosocial interventions include both patient education and psychotherapy. It is important for patients to receive social support and illness management skills. Family and friends must be aware of the high rates of social dysfunction and marital discord. Involvement in national support groups is advisable (National Depressive and Manic-Depressive Association).

Psychoeducation usually focuses on:

- Assessment of what parameters will have an impact on the outcome of patient's disease.
- Implementing the boundaries and requirements of treatment.
- Implementation of a personal cost-benefit analysis concerning specific treatment directions.
- Implementing a follow-up program.
- Implementing future directions, which may include adjustment or change interventions.

Genetic counseling should be a part of family education programs since the predisposition of this disorder has been genetically proven to increase among first-degree relatives.

Prognosis

Overall the long-term outcome for BT II patients is variable. Patients must maintain strict compliance with medications. Psychotherapy and education can assist the patient and family members with pertinent information concerning relapses, noncompliance with prescription medications, and specific adjustments necessary for the welfare of the affected individual. Patients taking psychotropic medications must understand the importance of regular dosing as prescribed and the necessity for constant psychiatric follow up visits. In comparison to major depression (Unipolar), BT II depression is usually associated with longer depression, more severe depressive symptoms, more relapses (having active symptoms return after a period of remission) and experience more incapacitation and hospitalization. Some studies have shown that early onset BT II is associated with more recurrences, but not necessarily worse outcomes.

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ORGANIZATIONS

National Depressive and Manic-Depressive Association. 730 N. Franklin, Suite 501, Chicago, IL 60610-7204. (800) 826-3632 or (312) 642-7243. <http://www.ndmda.org>.

WEBSITES

American Psychological Association. <http://helping.apa.org/>.

National Mental Health Organization. <http://www.nmha.org>.

Laith Farid Gulli, MD

Bloch-Sulzberger syndrome *see* **Incontinentia pigmenti**

Bloom syndrome

Definition

Bloom syndrome is a rare inherited disorder characterized primarily by short stature and a predisposition to various types of **cancer**. It is always associated with a decreased stability in the **chromosomes** that can be seen by cytogenetic laboratory techniques.

Description

Bloom syndrome (BS) was first described by D. Bloom in 1954. The clinical symptoms of BS include small body size, sun-sensitive skin that is prone to a reddish rash, patchy spots on the skin that are either lighter or darker than the expected skin color, severe immune deficiency, and an enormous predisposition to various types of cancer. The hallmark of the disorder is genetic instability that manifests itself in chromosomes that tend to exchange material with one another.

Genetic profile

BS is inherited in an autosomal recessive manner. The **gene** responsible for this disorder is known as BLM and it is located on chromosome 15, in band q26.1. Changes or mutations in the BLM gene lead to decreased stability in the chromosomes. Chromosomes of people with BS will show an increased amount of gaps, breaks, and structural rearrangements.

The most characteristic chromosomal abnormality in BS involves the tendency for deoxyribonucleic acid (**DNA**) strands to exchange material, most likely during replication. DNA is the molecule that encodes the genetic information and determines the structure, function, and behavior of a cell. The exchange of DNA may occur between a *chromatid* of each of the two homologues of a chromosome pair, forming a unique structure called a *quadriradial*, or between the two sister chromatids of one chromosome, known as sister-chromatid exchange (SCE).

The BLM gene produces the BLM protein. The BLM protein is a member of the helicase family and is thus capable of unwinding DNA and **RNA**. This unwinding process provides single stranded templates for replication, repair, recombination, and transcription. Additionally, the BLM protein may function in a post-replication recombination process that resolves errors generated during replication. Mutations (changes) prevent the BLM gene from making BLM protein. Without adequate amounts of this protein, errors are likely to occur in these important processes and these errors are less likely to be repaired.

KEY TERMS

Carcinoma—Any cancer that arises in the epithelium, the tissue that lines the external and internal organs of the body.

Chromatid—Each of the two strands formed by replication of a chromosome. Chromatids are held together by the centromere until the centromere divides and separates the two chromatids into a single chromosome.

Erythema—Redness of the skin due to dilatation of capillaries.

Fecal blood testing—Examination of the stool for any evidence of blood, which may be a sign of cancers in the digestive tract.

Homologues—Chromosomes or chromosome parts identical with respect to their construction and genetic content (i.e. the two chromosome #1s are homologous, as are the two #2s, #3s, etc...).

Leukemia—Cancer of the blood forming organs which results in an overproduction of white blood cells.

Lymphoma—A malignant tumor of the lymph nodes.

Sigmoidoscopy—The visual examination of the inside of the rectum and sigmoid colon, using a lighted, flexible tube connected to an eyepiece or video screen for viewing.

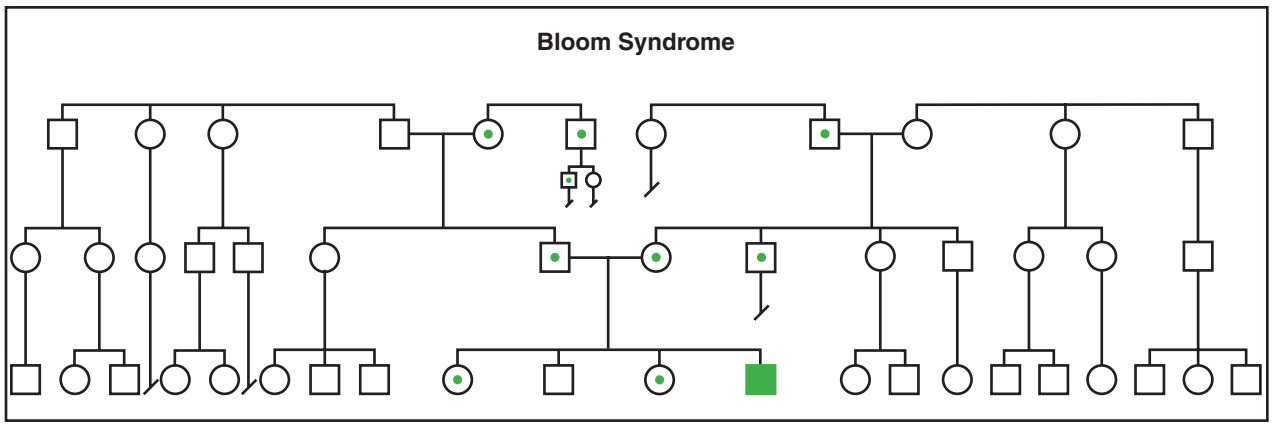
Telangiectatic—A localized collection of distended blood capillary vessels.

As of 2001, it is known that mutations in the BLM gene lead to the symptoms of BS. However, the precise relationship between these mutations and the symptoms seen in BS is still unknown.

Additionally, the DNA of individuals affected with BS is much more prone to spontaneous mutations, perhaps because the inadequate amount of BLM hinders the correction of these errors.

Demographics

BS is a very rare condition, thought to affect a very small proportion of the general population (approximately 1/6,330,000). However, in the Ashkenazi Jewish population, approximately 1/60,000 people are affected with BS. Approximately 1/100 people of this ethnic group are carriers of a mutation in the BLM gene. These carriers do not have BS but are capable of passing it on to



(Gale Group)

their children if the other parent is also a carrier. If both parents are carriers, each pregnancy will have a 25% chance of being affected with the disorder. Carriers, or individuals with only one copy of the abnormal gene, do not appear to have an increased risk for cancer or other symptoms associated with BS. They have near normal or normal genetic stability.

Signs and symptoms

There are two characteristic signs that are seen in nearly all individuals with BS. The first is an overall small body size, which is usually noted at birth and continues throughout the person's lifetime. The growth deficiency is often accompanied by a small brain and head. The head may be *dolichocephalic* as well, meaning that is it elongated from the front to the back of the head. The average height for an adult with BS is 147.5 cm for males and 138.6 cm for females.

The second characteristic that is very common in individuals with this disorder is an enormous predisposition to cancer. Both *benign* (non-cancerous) and *malignant* (cancerous) tumors arise at an early age and with great frequency in a wide variety of body locations and cell types. Thirty-seven percent of patients have malignant tumors. The mean age at diagnosis of a cancer is 24 years with a range of 2–46 years. Lymphomas and leukemias are common and generally appear before the age of 25. Carcinomas are common as well, usually appearing after the age of 20, most often in the colon, skin, breast, or cervix. Cancer is the most common cause of death for individuals with BS. Radiation treatment or chemotherapy can lead to further complications in these patients due to the increased sensitivity to exposures that may damage their fragile chromosomes.

There are additional features that may or may not be present in individuals with BS and they vary in severity from person to person. In some cases of BS, the person may have some unique facial features, including a narrow, triangular face shape, a prominent nose, a small jaw, and protuberant ears. The voice may be high pitched and somewhat squeaky in tone.

Infants may experience repeated respiratory tract infections, ear infections, and vomiting and diarrhea that can lead to a life-threatening loss of body water (dehydration). Additionally, after the first significant exposure to sunlight, an infant may develop a reddish "butterfly rash" on the cheeks and nose described as erythematous or telangiectatic. The severity of the rash can vary from a faint blush during the summertime to a severely disfiguring, flaming red lesion. Rarely, other areas of the body that are exposed to sunlight can show a similar rash. In childhood, the skin may begin to appear "patchy" showing some spots with less pigment than the rest of the skin (hypopigmentation) and some with more pigment than the rest of the skin (hyperpigmentation).

Men diagnosed with this disorder may have abnormally small testes and might be unable to produce sperm, making them infertile. Women can have early menopause and often have reduced fertility.

Individuals with BS have a higher incidence of **diabetes mellitus** when compared to the general population. The average age of onset of diabetes is 25 years, earlier than the usual age of onset of type II diabetes and later than that of type I. Additionally, this disorder can lead to a compromised immune system, resulting in an increased susceptibility to bacterial infections. Infections of the respiratory tract and ears are seen most commonly.

Intelligence in individuals with BS seems to be average to low average. When they exist, limitations in intellectual abilities range from minimal to severe. Even when intelligence is normal in these individuals, there tends to be a poorly defined and unexplained learning disability

that is often accompanied by a short attention span. BS is often accompanied by a persistent optimistic attitude.

Diagnosis

BS can be suspected by the doctor but is generally confirmed by a cytogenetic study known as sister chromatid exchange (SCE) analysis. This disorder is the only one that features an increased risk of SCE. This analysis is indicated in any child or adult with unexplained growth deficiency regardless of whether or not other features of the BS are present.

SCE analysis involves taking a blood sample, treating it with a special process in the laboratory, and examining the chromosomes. In individuals with BS, the chromosomes will show an approximately 10-fold increased rate of sister chromatid exchange. Most likely, unique chromosome structures called quadriradials will also be visible in a higher frequency than expected. SCE and quadiradials are present in untreated cells from individuals without BS, although much less frequently.

In addition to examining the chromosomes, it is also possible to look for specific changes in the BLM gene. This type of evaluation is generally used only for those who may be carriers of the **gene mutation** rather than those who are suspected to have the disorder. Carriers cannot be identified by SCE analysis because they do not show an increased rate of SCE.

Carrier testing is available for the Ashkenazi Jewish population. In these individuals, there is one particular mutation in the BLM gene that is responsible for most cases of BS. A blood sample can be tested for the presence of this mutation. Almost all Ashkenazi Jewish carriers of the BS gene can be identified in this manner. The great majority of carriers of the mutation causing BS are of Ashkenazi Jewish descent and, thus, this test is designed for that high-risk population. The test is not accurate for people from other ethnic populations in whom the specific changes of the BLM gene are not so well understood.

Prenatal diagnosis is available for carrier couples with previously identified mutations in the BLM gene.

It is thought that BS is highly underdiagnosed. Many affected individuals are treated for a symptom or are mistakenly considered to have another rare disorder.

Treatment and management

There is no treatment for BS—the underlying genetic defect cannot be repaired. However, early diagnosis and management can increase the life span of these individuals.

Babies and young children with BS are often poor eaters. Thus, nutritious food and multivitamins may help improve growth. Treatment with growth hormone has been attempted in several cases but has been generally unsuccessful. Further investigation into this possibility has been limited due to reports that cancer has developed in conjunction with growth hormone treatment.

The reddish skin lesions can be controlled by avoiding the sun, wearing a hat or bonnet, and by using a sunscreen. Avoidance of sun exposure is most critical in the first few years of life, since the severity of the skin lesion appears to be established at that time.

Cancer surveillance is of utmost importance in BS. After the age of 20, annual sigmoidoscopy and fecal blood testing are recommended, as well as breast self-examinations and pap smears for women. It is suggested that the individual be followed closely by a specialist or clinic knowledgeable about BS so that any subtle symptoms of carcinomas can be treated. Early surgical removal of these tumors provides the best chance of a cure. Individuals may wish to store their bone marrow early in life in case a later treatment diminishes their existing bone marrow. Unfortunately, early diagnosis of leukemia is not known to improve the chances of curative therapy; thus, surveillance of the blood and blood-forming tissues in children with BS is not recommended as a part of the cancer surveillance.

Additionally, individuals with this disorder are instructed to avoid x rays, chemotherapeutic drugs and other environmental exposures that may damage their unusually fragile chromosomes. Due to the immunodeficiencies often associated with BS, it is important to treat any bacterial infections promptly.

Prognosis

The mean age at death is 23 years with a range from 1–48 years. Cancer is the most common cause of fatalities in individuals with BS and is thought to be responsible for approximately 80% of deaths. Chronic respiratory infection is the next most common cause of death.

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Mary E. Freivogel, MS

Blue rubber bleb nevus syndrome

Definition

Blue rubber bleb nevus syndrome (BRBNS) is a rare disorder characterized by hemangiomas of the skin and gastrointestinal (GI) tract. Hemangiomas are benign or noncancerous tumors of newly formed blood vessels and skin. This syndrome derives its name from these distinctive rubber-like skin lesions.

Description

In 1860 G. G. Gascoyen first reported the association of cutaneous or skin nevi and intestinal lesions with GI bleeding. William Bean in 1958 first used the term BRBNS to describe the rubber-like tumors. Because of his description, BRBNS is sometimes called Bean syndrome. Besides the skin and GI tract, nevi are found on all internal organs and even the brain. Nevi are birthmarks of the skin that are probably hereditary because they are not caused by external factors.

Genetic profile

To date, the **gene** that causes BRBNS has not been identified. The fact that it has not been discovered does not imply the gene does not exist. Some cases of BRBNS are familial and support an autosomal dominant form of **inheritance**, meaning that only one copy of the non-working gene is required to manifest the condition. An affected parent has a 50% chance of passing the disorder to his or her offspring. However, most cases are sporadic without a familial tendency.

Demographics

Less than 180 cases have been reported worldwide. BRBNS affects all races, both sexes, and may be present at birth. The effects on life expectancy are unknown because so few cases exist.

Signs and symptoms

The distinctive blue skin blebs are the hallmark of BRBNS and are not cancerous. Blebs are nevi that measure more than 5 mm around. Composed of skin and large dilated blood vessels, the nevi do not disappear and are found on internal organs such as the stomach, liver, spleen, heart, bone, muscle, bladder, and vulva. They are easily compressible and refill after compression. Occasionally, the nevi are painful. Ranging in size from millimeters to several centimeters, the nevi can number from a few to hundreds. As the patient ages, they can increase in size and number. In rare cases, large lesions can cause skeletal deformities that may lead to amputation.

Nevi are usually present at birth. Sometimes, however, they may not appear until ages two or three.

Patients with BRBNS develop an extreme paleness or pallor of the skin. This paleness results because anemia, a low blood count, decreases the amount of oxygen available to the surface skin. Often they complain of fatigue that results from low iron stores and the anemia.

Chronic or acute bleeding in the GI tract may be detected when blood is present in the stool. Chronic bleeding causes anemia, pallor, fatigue, and low iron stores. Iron supplements will help to increase the blood count. Acute bleeding in the GI tract happens quickly and can rapidly decrease a normal blood count. Immediate blood transfusion or surgery to remove the bleeding nevus can correct this condition.

Diagnosis

The first key to diagnosis of this condition is the appearance of the skin nevi. If they do not have the distinct rubbery texture, blue color, and refill after they have been compressed, another diagnosis should be considered. Endoscopy is required to examine the GI tract for nevi. If they are present, then the diagnosis is confirmed. However, lack of nevi in the GI tract does not completely rule out BRBNS, since they may not develop until adolescence.

During an endoscopy a viewing instrument attached to a flexible tube is passed through the mouth to the small intestine. Or, the tube can be inserted through the rectum to the colon. The doctor can then examine the GI tract for nevi.

A patient will require blood tests to assess anemia and iron deficiency as well as a stool test for the presence of blood. Although nevi may be found on the brain, few patients have neurological signs such as seizures or partial paralysis.

Treatment and management

Treatment of BRBNS will depend upon the severity, number, size, and location of the nevi. Skin lesions that are life-threatening can be safely removed by surgery, or laser therapy. The severity of bleeding from GI lesions will determine how they are treated. Surgery can remove single lesions; however, the number may be too great to excise them all. Treatment methods that are less invasive than surgery use endoscopy to tie off bleeding nevi.

Patients who have neurological signs should have a magnetic resonance image (MRI) of the brain to discover the extent of nevi. Seizures can usually be controlled by medications. Physical therapy may improve paralysis.

Prognosis

Although BRBNS is a chronic, progressive disease it does not appear to be fatal. If the GI bleeding and anemia are treated, the patient will usually cope well. If a patient expresses concerns about his or her physical appearance psychological counseling should be considered.

Resources

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ORGANIZATIONS

Nevus Network, The Congenital Nevus Support Group. PO Box 1981, Woodbridge, VA 22193. (703) 492-0253. <http://www.nevus.org>.

Nevus Outreach, Inc. 1616 Alpha St., Lansing, MI 48910. (517) 487-2306. <http://www.nevus.org>.

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Suzanne M. Carter, MS, CGC

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Cutaneous—Of, pertaining to, or affecting the skin.

Endoscopy—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

Nevus—Any anomaly of the skin present at birth, including moles and various types of birthmarks.

Brachmann-de Lange syndrome *see* **Cornelia de Lange syndrome**

Brachydactyly

Definition

Brachydactyly (BD) refers to shortening of the fingers or toes due to underdevelopment of the bones in the hands or feet.

Description

The word brachydactyly comes from the Greek terms *brachy*, meaning "short," and *daktylos*, meaning "digit." This term is used to describe the hands and feet of people who have shortened digits (fingers or toes). The digits themselves may be shorter than normal, or they may appear small because of shortening of the other bones in the hands or feet. This shortening occurs when one or more of the hand or foot bones fail to develop or grow normally.

BD is usually isolated, meaning that it is not associated with any other medical problems. BD may occur along with other physical differences or health problems, often as part of a "syndrome."

BD occurs in a variety of patterns, depending upon which hand or foot bones are affected and how severely they are shortened. It is important to know some basic information about the bone structure of the hands and feet in order to understand the various patterns of BD. Beyond the wrist and ankle, each hand and foot contains 19 tube-shaped (tubular) bones in a specific arrangement. For purposes of orientation, the fingers and toes are numbered from one (thumb or great toe) to five (little finger or little toe). When a fist is made, the bones in the hand that extend from the wrist to the knuckles are called metacarpals. There are five metacarpals, one for the thumb (first metacarpal) and each finger. Each thumb and finger contains several bones called phalanges. A single one of these bones is called a phalanx. The phalanges are arranged end to end and are separated by joints. The thumb has two phalanges and each finger has three phalanges. The phalanges within a particular finger are named according to their location. The phalanges closest to the metacarpals are called the "proximal" phalanges, those in the middle of the fingers are called the "middle" phalanges, and those at the ends of the fingers are called the "distal" or "terminal" phalanges. The thumbs have only proximal and distal phalanges.

The foot bones are very similar to the hand bones. Like the metacarpals, there are five metatarsal bones that extend from the ankle to each of the toes. The bones in the toes are also called phalanges. There are two phalanges in the great toe and three phalanges in each of the other toes.

BD can involve any of the phalanges, metacarpals, and metatarsals in many different combinations. The shortening of these bones may range from mild to severe. Sometimes certain bones are completely absent. Shortening of the bones may occur in one, several, or all of the digits. For a particular finger or toe, the entire digit may be short or only a particular phalanx may be underdeveloped. When BD involves the distal phalanges, the fingernails or toenails may be small or absent. A digit may also be of normal length but appear short due to shortening of its corresponding metacarpal or metatarsal bone. Reduced length of a metacarpal bone is often easiest to appreciate when the hand is held in a fist.

BD can also occur with other abnormalities of the hands and feet. When a phalanx is abnormally shaped, the finger or toe may be bent to one side (clinodactyly). Sometimes the digits have webbing between them (syndactyly). The phalanges may also be fused together at their ends (symphalangism). This makes it difficult to bend a digit at the joint where the phalanges are fused.

BD frequently occurs in characteristic patterns that can be inherited through families. These patterns are classified as particular types of BD, depending upon which bones and which digits of the hands and/or feet are shortened. There are several classification systems used to describe these different types of BD. The system that is used most frequently was developed by Dr. Julia Bell in 1951 and is called the "Bell Classification."

There are five main types of BD in the Bell Classification, which are designated types A through E. Their major features are as follows:

- In type A, the *middle phalanges* of one, several, or all of the fingers and/or toes are shortened. This form of BD is further divided into types A1, A2, and A3. In type A1, the middle phalanges of *all digits* and the proximal phalanges of the thumbs and great toes are shortened. People with this form of BD generally have hands and feet that appear small with relatively equal shortening of all digits. In type A2, the middle phalanges of the *index finger and second toe* are shortened and often abnormally shaped. In type A3, the middle phalanx of the *fifth finger* is shortened and this finger often bends toward the fourth finger. Several other forms of BD type A have also been described.
- In type B, the *distal phalanges and nails* of the fingers and/or toes are small or absent. The middle phalanges may also be shortened, and the tips of the thumbs and/or great toes may be broad or have a "duplicated" (double) appearance. In this type of BD, the digits typically look as though their tips have been amputated.
- In type C, the *middle phalanges* of all of the fingers may be shortened, but the fourth finger is least affected and is often the longest finger. The index and middle fingers may be bent toward the fourth finger. The first metacarpal bone can also be short, making the thumb appear small.
- In type D, the *distal phalanges of the thumbs and/or great toes* are shortened and broad.
- In type E, the *metacarpals and/or metatarsals* are shortened. The fourth and fifth metacarpals and metatarsals are most commonly shortened, but any of them may be affected.

Genetic profile

Many different genetic signals are required for normal formation of the hand and foot bones. BD is usually caused by abnormalities in these genetic blueprints. Sometimes BD can be caused by exposure to drugs or medications taken during pregnancy. Problems with

blood flow to the hands or feet during fetal life may also cause BD.

The types of BD in the Bell Classification are inherited in families from one generation to the next. Their pattern of **inheritance** is called autosomal dominant. This means that they are caused by abnormalities in only one copy of a **gene** from a particular gene pair. In fact, one form of BD (type A1) was the first human condition that was recognized to have this type of inheritance pattern. Autosomal dominant forms of BD can be inherited by a child of either sex from a parent of either sex. The gene change causing BD may also occur in a particular person for the very first time within a family. Each child born to a person having autosomal dominant BD has a 50% chance of also having BD. However, the degree of hand or foot abnormalities can be very different between people with the same type of BD, and even among members of the same family.

Until recently, nothing was known about the genes that cause BD. This has changed with the identification of the genes that cause two forms of autosomal dominant BD (types B and C) in the past several years. The gene causing BD type C was the first to be identified in 1997. The name of this gene is the "Cartilage Derived Morphogenetic Protein 1" gene, abbreviated as CDMP1. This gene is located on the long arm of chromosome 20 (at location 20q11.2) and provides an important genetic signal to the developing bones of the limbs. Most people with BD type C have abnormalities in one of their two copies of this gene.

The gene causing BD type B was identified in 2000. This gene is called ROR2 and is located on the long arm of chromosome 9. Like CDMP1, ROR2 also provides an important genetic blueprint for the normal development of bones. BD type B is caused by alterations in one copy of this gene.

One interesting feature of the CDMP1 and ROR2 genes is that they can also cause other medical conditions with bone problems that are much more severe than BD. This happens when both copies of either gene are altered in the same person. The genes for other types of autosomal dominant BD have not yet been discovered.

Demographics

BD occurs in people of many different racial and ethnic backgrounds. It is difficult to determine the overall frequency of BD in the general population because many people who have BD never seek medical attention for their shortened digits. Types A3 and D are the most common forms of BD, but their frequencies vary widely between groups of people from different backgrounds. For example, type A3 has been found in fewer than 1% of Americans, compared to 21% of Japanese people. Because isolated forms of BD are generally inherited as autosomal dominant traits, they should affect males and females in equal numbers. However, several types of BD may be more common in females.

KEY TERMS

Clinodactyly—An abnormal inward curving of the fingers or toes.

Digit—A finger or toe. Plural–digits.

Metacarpal—A hand bone extending from the wrist to a finger or thumb.

Metatarsal—A foot bone extending from the ankle to a toe.

Phalanges—Long bones of the fingers and toes, divided by cartilage around the knuckles.

Symphalangism—Fusion of phalanges at their ends.

Syndactyly—Webbing or fusion between the fingers or toes.

Signs and symptoms

BD is often evident at birth, but may also develop or become more obvious during childhood. It usually does not cause pain or other physical symptoms. In fact, many people who have BD consider it to be a normal family trait rather than a medical condition. When BD does cause problems, they are usually related to the size, appearance, or function of the hands or feet. The altered appearance of the hands or feet may make persons with BD feel self-conscious. Shortening of the digits may also make it difficult to find comfortable shoes or gloves. In its severe forms, BD may affect a person's ability to grip objects or participate in certain jobs or leisure activities. Hand function may be especially affected when BD is associated with clinodactyly, syndactyly, or symphalangism. When BD is associated with significant deformities of the feet, walking may be difficult or painful.

In some cases, BD occurs in combination with other physical changes or medical problems. For instance, people with autosomal dominant forms of BD are often shorter than expected and may have other alterations of the skeleton besides short digits. Some people with BD type E also have hypertension (high blood pressure). BD may also be present as one finding in a number of different genetic conditions (syndromes).

Diagnosis

The diagnosis of BD is made when a person has shortening of the digits due to lack of normal growth and development of one or more bones in the hands or feet. When the bones are significantly shortened, this is easily noticed in the appearance of the hands and feet. When the shortening is mild, it may only be apparent on x rays. Some people may not realize that they have BD until told by a physician who has carefully examined their hands and feet.

X rays of the hands and feet are used to look at the bones in detail. A special analysis of the hand x rays called a "metacarpophalangeal profile" is often performed for people with BD. This involves measuring the length of each hand and finger bone. These measurements are then compared to the normal range of sizes for each bone. The metacarpophalangeal profile is used to identify particular patterns of BD. X rays may also reveal other bone changes that help to pinpoint a specific type of BD or another genetic condition. If a person has short stature or other bone changes, a series of x rays of the entire skeleton (skeletal survey) may be recommended.

Since BD is often inherited, detailed information about a person's relatives can be very important in evaluating someone with BD. A geneticist may wish to examine other family members or obtain x rays of their hands and feet. Because BD can occur in a variety of genetic conditions, a geneticist evaluating someone with BD will usually review his or her medical history and perform a detailed physical examination. The presence of other physical differences or medical problems may indicate that the brachydactyly is part of another condition rather than an isolated finding.

Laboratory tests are usually not helpful in diagnosing BD when it is an isolated finding. Although the genes for BD types B and C are known, testing of these genes is not routinely available or usually necessary. If a person with BD has signs or symptoms of another underlying condition, certain laboratory tests may be recommended. These tests may identify other associated medical problems or help to pinpoint a specific diagnosis.

Treatment and management

Many people who have BD are perfectly healthy and do not require any specific treatment for their hands and feet. When use of the hands is impaired, physical therapy or hand exercises may improve grip strength or flexibility. Evaluation by an orthopedist or physical therapist may also be helpful for people who have trouble walking comfortably due to bone changes in the feet. Surgery can be used to lengthen the hand or foot bones in some severe forms of BD. Surgery may also be helpful for people who have significant clinodactyly, syndactyly, or symphalangism. For most people with BD, however, surgery is not needed. If BD is associated with other medical problems, such as hypertension, specific treatments for these problems may be indicated.

Prognosis

Isolated BD generally has an excellent prognosis. When BD is associated with other health problems or is part of another condition, the overall prognosis depends upon the nature of the associated condition.

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David B. Everman, MD

Branchiootorenal syndrome

Definition

Branchiootorenal (BOR) syndrome is an autosomal dominant condition characterized by ear abnormalities, hearing loss, cysts in the neck, and kidney problems.

Description

The name branciootorenal syndrome describes the body systems most commonly affected by this genetic disorder. The term "branchio" refers to the abnormalities of the neck found in individuals with this syndrome.

Cysts (lump or swelling that can be filled with fluid) and fistulas (abnormal passage from the throat to the skin) in the neck occur frequently. The term "oto" refers to the ear disorders associated with the syndrome. For example, the outer ear can be unusual in appearance. Hearing loss is also common. Finally, the term "renal" stands for the kidney problems commonly seen in patients with this condition. These can be very mild or very severe, as can any of the symptoms associated with this disorder.

Dr. M. Melnick first described branchiootorenal (BOR) syndrome in 1975. Another name for BOR syndrome is Melnick-Fraser syndrome. Individuals with BOR syndrome typically have physical differences that are present at birth (congenital). These birth defects are caused by a change (mutation) in a **gene**.

Genetic profile

Scientists recently discovered that mutations in the EYA1 gene cause BOR syndrome. The EYA1 gene is located on chromosome 8. The exact function of the EYA1 gene is unknown, but mutations in this gene disrupt normal development, producing the physical differences common to BOR syndrome. A mutation in this gene can affect the normal development of the ear, kidney, and the branchial arches. The branchial arches are tissues that develop very early in pregnancy and are involved in the formation of the face and neck.

BOR syndrome is inherited in a dominant manner. This means that only one gene in the pair must be mutated in order for the individual to be affected. If a person has a mutation in one of their EYA1 genes, the disorder is typically present. The characteristics of the syndrome can be extremely variable in severity.

A mutation in the EYA1 gene may be inherited from a parent with BOR syndrome. A mutation can also occur by chance, in an individual without a family history of BOR syndrome. If a child inherits an abnormal gene from a parent, the signs of the disorder can be very different between the parent and the child. This is called *variable expressivity*. For example, a parent who has a very mild form of BOR syndrome can have a severely affected child. The reverse situation can also occur.

Once an individual has a mutation in the EYA1 gene, there is a 50/50 chance with each pregnancy that the gene will be passed on. This means that there is a 50/50 chance of having a child with BOR syndrome. Male and female children have the same risk. It does not matter if the gene is inherited from the mother or the father.

Demographics

BOR syndrome occurs in one of every 40,000 live births. BOR syndrome is seen in all ethnic groups and

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Bilateral—Relating to or affecting both sides of the body or both of a pair of organs.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Congenital—Refers to a disorder which is present at birth.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Ear tags—Excess pieces of skin on the outside of the ear.

Fistula—An abnormal passage or communication between two different organs or surfaces.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Gustatory lacrimation—Abnormal development of the tear ducts causing tears when chewing.

Lacrimal ducts—Tear ducts.

Microtia—Small or underdeveloped ears.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

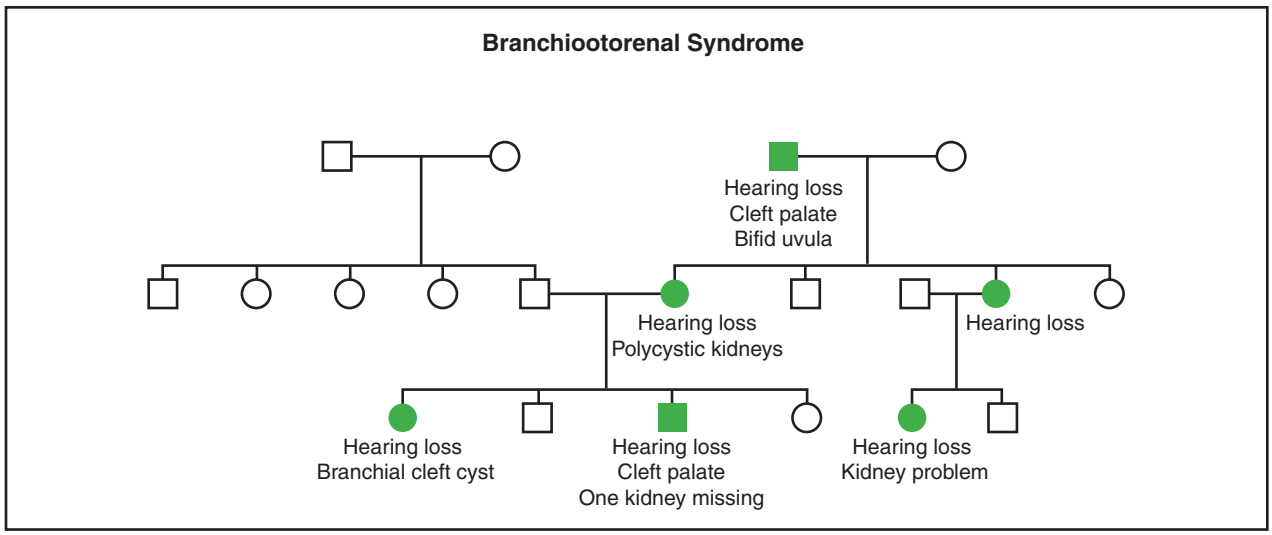
Preauricular pits—Small pits in the skin on the outside of the ear.

Renal agenesis—Absence or failure of one or both kidneys to develop normally.

Renal hypoplasia—Abnormally small kidneys.

Unilateral—Refers to one side of the body or only one organ in a pair.

Variable expressivity—Differences in the symptoms of a disorder between family members with the same genetic disease.



(Gale Group)

cultures. It also affects males and females equally. One study suggested that 2% of individuals with severe hearing loss have BOR syndrome.

Signs and symptoms

The characteristics associated with BOR syndrome are highly variable. Some individuals with BOR syndrome have many physical deformations. Other individuals with BOR syndrome have a few minor physical differences. The birth defects can occur on only one side of the face (unilateral) or be present on both sides (bilateral).

Abnormal development of the ears is the most common characteristic of BOR syndrome. The ears may be smaller than normal (microtia) and may have an unusual shape. Ear tags (excess pieces of skin) may be seen on the cheek next to the ear. Preauricular pits (small pits in the skin on the outside of the ear) are found in 75% of patients with BOR syndrome. Hearing loss is present in 85% of individuals with BOR syndrome and this loss may be mild or severe.

The most distinctive finding in individuals with BOR syndrome is the presence of cysts or fistulas in the neck region due to abnormal development of the branchial arches. These cysts and fistulas can be filled with or discharge fluid.

Approximately two-thirds of individuals with BOR syndrome also have kidney abnormalities. These abnormalities can be very mild and cause no health problems, or they can be very severe and life threatening. The kidneys can be smaller than normal (renal hypoplasia), abnormally shaped, malfunctioning, or totally absent (renal agenesis).

Other less common characteristics associated with BOR syndrome include cleft palate, facial nerve paralysis, and abnormalities of the tear ducts. The tear ducts (lacrimal ducts) may be absent or abnormal. Some patients with BOR syndrome uncontrollably develop tears while chewing (gustatory lacrimation).

Diagnosis

The diagnosis of BOR syndrome is made when an individual has the common characteristics associated with the condition. An individual does not need to have all three components of the disorder in order to be diagnosed with the condition.

There is no readily available genetic test that can diagnose BOR syndrome. Some laboratories are performing DNA testing for mutations in the EYA1 gene, however, this testing is currently being offered on a research basis only. Individuals interested in this type of testing should discuss it with their doctor.

Treatment and management

Once a child is diagnosed with BOR syndrome, additional tests should be performed. A hearing evaluation is necessary to determine if there is hearing loss. If hearing loss is evident, the child should be referred to a hearing specialist. Hearing tests may need to be performed on a regular basis. Speech therapy may also be helpful. An ultrasound of the kidney may be necessary, due to the increased risk for birth defects in these areas.

Finally, minor surgery may be required to correct the branchial cysts and fistulas commonly found in BOR syndrome.

Prognosis

The prognosis for individuals with BOR syndrome is very good. Individuals with BOR syndrome typically have a normal life span and normal intelligence.

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ORGANIZATIONS

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

National Kidney Foundation. 30 East 33rd St., New York, NY 10016. (800) 622-9010. <http://www.kidney.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Research Registry for Hereditary Hearing Loss. 555 N. 30th St., Omaha, NE 68131. (800) 320-1171. <http://www.boystown.org/btnrh/deafgene.reg/waardsx.htm>

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Holly Ann Ishmael, MS

Breast cancer

Definition

Breast cancer is a disease in which abnormal breast cells begin to grow uncontrollably, forming tumors. It often shows up as a breast lump, breast thickening, or skin change.

Description

The breasts are areas of tissue located on the front chest wall, and are essentially part of the skin. They are like "specialized sweat glands" in their structure and function, in that they can produce and secrete fluids, like milk. They are made of ductal tissue, supporting connective tissue, and fat. The breasts naturally drain fluid through the lymph channels to the axillary lymph nodes, located in the armpit areas. Within the breasts are intricate structures of ducts and lobules, which are channels and areas that create and transport milk during lactation.

Excluding skin cancers, breast cancer is the most common cancer among women and the leading cause of death in women in their middle years of life (as of 2000). Male breast cancer, though rare, accounts for less than 1% of all breast cancers. Both genetic and environmental factors are thought to cause breast cancer. Of all breast cancer diagnoses, only approximately 5-10% are caused by hereditary factors like specific alterations in breast cancer susceptibility genes, or by a genetic cancer syndrome. In these instances, individuals may have a strong family history of cancer and the cancers may be diagnosed at an earlier age than usual.

Breast cancers vary in their type and size, and this can be determined by a breast biopsy. Breast cancer may commonly be detected by a mammogram, a physician's clinical breast examination (CBE), or a patient's own breast self- examination (BSE). Breast cancer, if it is the first cancer diagnosed, may sometimes metastasize (spread) to other organs, such as the liver, bone, lungs, skin, or brain. The breasts may also be the site of metastasis from other primary cancers.

Breast cancer may present as a lump or other change within the breast. As with other types of cancer, the initial diagnosis may be unexpected. Each cancer has a unique prognosis, and this will affect the patient's concern. If an individual has a very strong family history of breast cancer, the diagnosis may be somewhat expected, but no less emotionally taxing. Treatment and management of the cancer may be extremely exhausting, painful, and stressful for the patient and his or her family.

Genetic profile

Cells in breast tissue normally divide and grow, according to controls and instructions of various genes. If these genes have changes within them, the instructions for cellular growth and division may go awry. Abnormal, uncontrolled cell growth may occur, causing breast cancer. Therefore, all breast cancers are genetic because they all result from changes within genes. However, most breast cancers occur later in life after years of exposure to various environmental factors that can cause alter-

KEY TERMS

Alteration—Change or mutation in a gene, specifically in the DNA that codes for the gene.

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Bilateral breast cancer—Cancer of both breasts, caused by two separate cancer processes.

Bile—A substance produced by the liver, and concentrated and stored in the gallbladder. Bile contains a number of different substances, including bile salts, cholesterol, and bilirubin.

Breast biopsy—Small sample of tissue taken from the breast and studied, to diagnose and determine the exact type of breast cancer.

Breast self-exam (BSE)—Examination by an individual of their own breasts.

CA-125 (Carbohydrate antigen 125)—A protein that is sometimes high when ovarian cancer is present. A blood sample can determine the level of CA-125 present.

Clinical breast exam (CBE)—Examination of the breasts, performed by a physician or nurse.

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

Mammogram—A procedure in which both breasts are compressed/flattened and exposed to low doses of x rays, in an attempt to visualize the inner breast tissue.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Multifocal breast cancer—Multiple primary cancers in the same breast.

Primary cancer—The first or original cancer site, before any metastasis.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

ations (such as the body's own hormones, asbestos exposure, or smoking).

A small proportion of breast cancers is caused by inherited genetic alterations. In 1994 a breast cancer susceptibility **gene**, known as BRCA1 (location 17q21), was identified. The discovery of BRCA2 (location 13q12) followed shortly in 1995. Women with alterations in these genes have an increased risk for breast and **ovarian cancer**, and men have an increased risk for **prostate cancer**. Men with a BRCA2 alteration have an increased risk for breast cancer. Slightly increased risks for colon and pancreatic cancers (in men and women) are associated with BRCA2 alterations.

BRCA1 and BRCA2 alterations are inherited in an autosomal dominant manner; an individual has one copy of a BRCA alteration and has a 50% chance of passing it on to each of his or her children, regardless of that child's gender. Nearly all individuals with BRCA alterations have a family history of the alteration, usually a parent. In turn, they also may have a very strong family history of breast, ovarian, prostate, colon, and/or pancreatic cancers. Aside from BRCA1 and BRCA2, there likely are other breast cancer susceptibility genes that are still unknown (such as BRCA3). Additionally, there may be other genes that convey increased risks solely for other cancers, such as ovarian cancer.

BRCA1 and BRCA2 are thought to function as "tumor-suppressor genes," meaning that their normal role is to prevent tumors from forming. Specifically, they control cellular growth and division, all the while preventing the over-growth that may lead to cancer. Alterations in tumor-suppressor genes, such as BRCA1 and BRCA2, would naturally lead to an increased risk of developing cancer. However, this risk is not 100%.

There are rare, genetic cancer syndromes that may include breast cancer. As a group, these comprise less than 1% of all breast cancer diagnoses. In these instances, an individual may have other health problems (unrelated to cancer) and a family history of a wide variety of cancers and symptoms. These health problems can initially appear unrelated, but may be caused by alterations in a specific gene. As an example, Cowden syndrome typically involves early-onset thyroid and breast cancers, as well as specific tissue growths on the face, limbs, and mouth. An individual with Cowden syndrome may have all or some of these symptoms. It is now known that alterations in the PTEN gene cause Cowden syndrome. Other known cancer syndromes are caused by specific alterations in different genes. These genes are responsible for the various symptoms and cancers in an individual.

Demographics

On average, a North American woman faces a lifetime risk of approximately one in nine (11%) to develop breast cancer. Most cases of breast cancer occur in women past the age of 50, and more commonly in individuals of North American descent.

As of 2000, the prevalence of BRCA alterations in the general population is estimated to be between 1/500 and 1/1,000. However, there are specific alterations that are commonly found in certain ethnic groups. In the Ashkenazi (Eastern European) Jewish population, two specific BRCA1 alterations and one BRCA2 alteration

are commonly seen and range in prevalence from 0.1% to 1.0% in this group. As a result, hereditary forms of breast and ovarian cancer are more predominant in people of Ashkenazi Jewish ethnicity. A common BRCA1 alteration has been found in the Dutch population; a specific BRCA2 alteration exists in about 0.6% of people from Iceland. Additionally, common alterations have been identified in both BRCA1 and BRCA2 in French Canadians, and a BRCA1 alteration has often been seen in West Africans.

Signs and symptoms

Various symptoms may bring someone to medical attention in order to investigate the possibility of breast cancer. These may include a breast lump that persists, as opposed to one that only appears at certain times of a woman's menstrual cycle (which is more common). Other signs include changes from the normal breast shape, pain, itchiness, fluid leaking from the nipple (especially if a woman is not pregnant), a turned-in nipple, fatigue, or unexplained weight loss. Sometimes individuals may feel a breast lump or change while examining their own breasts, or a physician may note it on a CBE. Additionally, it may be seen on a screening mammogram. It is important to note that *not all* breast lumps or breast changes signify cancer—they may be benign growths or cysts that need to be removed or drained.

Signs of a possible BRCA1 or BRCA2 alteration in a family, signifying hereditary breast or ovarian cancer, include:

- several relatives with cancer
- close genetic relationships between people with cancer, such as parent-child, sibling-sibling
- earlier ages of cancer onset, such as before ages 45-50
- an individual with both breast and ovarian cancer
- an individual with bilateral or multi-focal breast cancer
- the presence of ovarian, prostate, colon, or pancreatic cancers in the same family
- case(s) of breast cancer in men

Suspicion of a BRCA alteration may be raised if someone has the above features in their family and they are of a particular ethnic group, such as an Ashkenazi Jew. This is because specific BRCA1 and BRCA2 alterations are known to be more common in this group of individuals.

Diagnosis

Once a suspicious breast abnormality has been found, the next step is determining if it is breast cancer. A mammogram can identify an area of increased breast density, which is a common sign of a malignant tumor. Women in their 20s to 30s naturally have denser breasts, so mammograms may not be as effective in this age group because the increased breast density associated with a tumor is difficult to see. Breast ultrasound, a way of visualizing the breast tissue using sound waves, can be helpful in younger women because breast density is not a large factor in its effectiveness. A breast biopsy can determine specifically whether the breast tissue has undergone a benign or malignant change because the breast tissue is studied directly under a microscope. Sometimes biopsies are performed with a very thin needle (known as fine needle aspiration), or with x ray guidance using a thicker needle (known as a core needle biopsy).

Newer techniques have improved breast cancer screening and diagnosis. Direct digital imaging in mammograms ends the need for film, and the digital images provide finer detail and allow the images to be rotated in order to get several different views of the breasts. Magnetic resonance imaging (MRI) uses magnetic energy to create an image. Its effectiveness is currently the subject of research studies, but MRI often provides very detailed imaging of tumors. MRI is expensive and this is another reason it is not widely used.

As of 2001, there is DNA-based **genetic testing** to identify a BRCA1 or BRCA2 alteration in an individual. In the United States, Myriad Laboratories in Utah is the only place to offer this costly testing (as of 2001, it is about $2,700 for initial analysis). A blood sample is used and both BRCA genes are studied for alterations. There is also targeted testing for people in high-risk ethnic groups (such as the Ashkenazi Jews) in which only the common BRCA alterations can be tested; this testing is much less costly. Even with current technology (as of 2001), only certain regions of the BRCA genes can be studied, which leaves some alterations unlocated.

With either method of testing, it is best to begin the testing process with an individual who has survived breast and/or ovarian cancer. This is because tests are more likely to find an alteration in a cancer survivor than someone who has not had cancer. A result is abnormal (or "positive") if a known cancer-causing BRCA alteration is found. If an alteration is found, it is assumed to have caused the cancer(s) in the tested, affected individual. That individual may also identify new cancer risks from the positive result. For example, if a woman survived breast cancer and was found to have a BRCA alteration through testing, she would now be at an increased risk to develop ovarian cancer, as well as a second breast cancer.

For people who go through testing and are not found to have a BRCA alteration (a "negative" result), this result is not informative. There are several possibilities

for a negative result. First, there could be a BRCA alteration in the family and the person did not inherit it. In this case, the cancer would be due to reasons unrelated to BRCA1 and BRCA2. Additionally, they could have an alteration in an unknown gene (such as BRCA3), for which there is no testing available (as of 2001). Lastly, they could have a BRCA1 or BRCA2 alteration that is undetectable by available testing methods.

There is a possibility that individuals may have an "unknown alteration" in one of their BRCA genes. In this scenario, a change in the **DNA** is identified, but its significance is unclear. Therefore, it is unknown whether the gene change causes cancer. In these situations, the results are most often considered uninformative, until more information about the alteration becomes available in the future.

Once an alteration is identified, other at-risk relatives, both affected and unaffected, can pursue targeted analysis for the confirmed familial alteration. This is much quicker and far less expensive than the initial analysis.

Unaffected individuals who test positive for a known alteration in the family are at a significantly increased risk to develop the associated cancers. A woman's risks associated with a BRCA1 alteration are: 3-85% for breast cancer by age 70, 40–60% for ovarian cancer by age 70. A man's risk with a BRCA1 alteration is about 8% for prostate cancer by age 70. A woman's risks with a BRCA2 alteration are: 4–86% for breast cancer by age 70, and 16–27% for ovarian cancer by age 70. Less than 1% of men with a BRCA2 alteration develop breast cancer but they are at a slight or moderate increased risk for prostate cancer. For BRCA2 in men and women, there is an increased risk for colon and pancreatic cancers. Cancers of the larynx (structure in neck that helps with breathing), esophagus (tube-like structure that connects mouth to stomach), stomach, gallbladder (structure that makes bile), bile duct (tube that transports bile between liver and intestine), blood, and melanoma (a form of skin cancer) have been seen in families with BRCA2 alterations.

When a person who has not had cancer tests negative for a known, familial BRCA alteration, they are lowered to the general risk to develop the associated cancers, such as the lifetime risk of 11% for a woman to develop breast cancer. This is because he or she did not inherit the genetic alteration causing cancer in his or her family.

Everyone should receive proper **genetic counseling** before pursuing any BRCA1 and BRCA2 testing. This should include asking them what they hope to learn from the testing. Many people are not aware of the testing limitations, and may be expecting a clear "yes/no" answer from the results. Asking people what they hope to learn from testing allows the opportunity to provide them with accurate facts, such as the possibility of a result that is not informative. Common motivations to be tested include the need to make informed medical decisions, financially planning for the future, or just "wanting to know" about cancer risk.

Genetic testing for cancer susceptibility often triggers strong emotional responses. It is important to find out about an individual's "support system" before they begin testing. Having a close friend, family member, or religious leader to talk with is often helpful for people pursuing testing. Someone who tests positive may be concerned because his or her risks for cancer are now higher than they were before the testing. Additionally, someone may feel "empowered" by the knowledge because they can better plan for medical procedures. Someone with a family history of a BRCA alteration may feel relief if they test negative, because they initially assumed they would develop cancer. Alternatively, someone who tests negative in this situation may feel "survivor guilt" for not having inherited the altered gene. All of these feelings may change the way an individual interacts with his or her family and friends. People may not be aware of the emotional changes that can occur from learning about cancer risk through genetic testing.

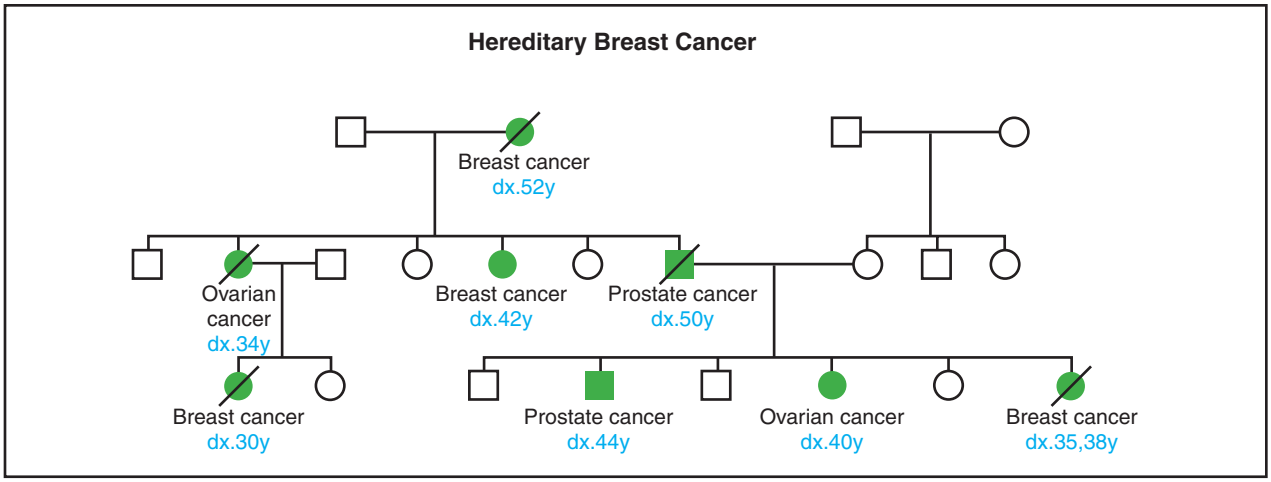
It is important to discuss the possibility of insurance coverage for the testing, particularly because it is so expensive. Insurance companies may not routinely cover the testing, unless a physician or genetic counselor describes the need for testing in a letter. Some companies are willing to cover the testing, without wanting to know the results.

Issues of potential "genetic discrimination" should be discussed. Unaffected individuals who test positive for a BRCA1 or BRCA2 mutation may face difficulty when trying to obtain health, life, and/or disability insurance. Fortunately, there are laws in place that can help protect American individuals who have group health insurance, but the exact laws vary by state. As of 2001, there are no laws to protect individuals from life and disability insurance discrimination, nor employer discrimination.

Treatment and management

Breast cancer treatment is determined by the exact size and type of cancer, so it is often unique to an individual. Treatment may include surgeries, such as a lumpectomy (removal of the breast lump) or mastectomy (removal of the entire breast). Breast reconstruction (re-creation of the breast) by plastic surgery is an option some individuals may pursue.

Chemotherapy, or using strong chemicals to kill fast-growing cells, is a common treatment. Side effects from



(Gale Group)

chemotherapy may include nausea, vomiting, hair loss, exhaustion, and sores in the mouth. Symptoms associated with menopause (such as "hot flashes" and the absence of menstrual periods) may occur, or menopause may actually begin because of chemotherapy. Radiation therapy is another common form of treatment, in which directed radioactive waves are used to kill fast-growing cells. Some side effects of radiation therapy are dry and itchy skin, rashes, exhaustion, nausea, and vomiting.

Sometimes, medications such as Tamoxifen are used to prevent a breast cancer from coming back. Tamoxifen is often used for five years following a breast cancer diagnosis to actively prevent a recurrence. Tamoxifen is only effective in specific types of breast cancer, which again are unique to each individual. Some side effects of Tamoxifen include beginning menopause, as well as an increased risk for uterine cancer. Other drugs, such as Raloxifene, are currently being studied for breast cancer prevention because it may be able to do the same things as Tamoxifen, without the side effects. Research studies are under way to determine whether Tamoxifen or Raloxifene can reduce the risk of breast cancer in women with BRCA alterations.

An example of a screening program for women at high risk to develop breast cancer includes:

- BSEs monthly starting in early adulthood (about 20–25 years of age)
- CBEs every six months or yearly starting at age 25–35
- mammograms yearly starting at age 25–35

Exact screening guidelines may vary between physicians. For men with a BRCA2 alteration, breast cancer screening is recommended, though no formal program is specifically recommended (as of 1997).

In addition to screening, women with BRCA1 or BRCA2 alterations should know about their preventive surgery options. They may consider having their healthy breasts and/or ovaries removed, in order to reduce their risks of developing breast and/or ovarian cancer. Women may be more agreeable to an oophorectomy because ovarian cancer is difficult to detect. Surgeries may greatly reduce a woman's cancer risk, but they can never eliminate the risk entirely.

For people with cancer or at high risk, there are support and discussion groups available. These may be invaluable to those who feel alone in their situation.

Prognosis

The type and size of breast cancer developed largely determines the overall prognosis for an individual. Those with larger tumors and those with a type of breast tumor that does not usually respond to treatment may have a poorer outcome. Additionally, once cancer has spread to other areas of the body, the prognosis worsens because the cancer is more difficult to treat. The cancer may also be more likely to continue spreading to other areas of the body.

As of 2001, those with BRCA alterations who develop breast cancer have a similar prognosis to those without BRCA alterations that have equivalent cancers. In addition, people with BRCA alterations are treated for their cancers using the same methods as those without alterations.

For cancer-free individuals identified to have BRCA alterations, it is important to remember that they are at an increased risk to develop the associated cancers, but that the risk is *not* 100%. Though people with BRCA alterations may feel "destined" to develop cancer, it is by no

means a certainty. It is also important to emphasize that breast cancer screening techniques and treatments are constantly being evaluated and improved.

Resources

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

Facing Our Risk of Cancer Empowered (FORCE). 934 North University Drive, PMB #213, Coral Springs, FL 33071. (954) 255-8732. info@facingourrisk.org. <http://www.facingourrisk.org>.

The National Alliance of Breast Cancer Organizations. 9 East 37th Street, 10th Floor, New York, NY 10016. (888) 806-2226 or (212) 889-0606. NABCOinfo@aol.com. <http://www.nabco.org>.

Susan G. Komen Breast Cancer Foundation. Occidental Tower, 5005 LBJ Freeway, Suite 370 LB74, Dallas, TX 75244. (800) 462-9273 (Hotline) or (214) 450-1777. helpline@komen.org. <http://www.breastcancerinfo.com>.

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"The Genetics of Breast and Ovarian Cancer." *CancerNet.* <http://cancernet.nci.nih.gov/clinpdq/cancer_genetics/Genetics_of_breast_and_ovarian_cancer>.

Deepti Babu, MS

Broad-thumb-hallux syndrome *see* **Rubinstein-Taybi syndrome**

Bruton agammaglobulinemia

Definition

Bruton agammaglobulinemia is an X-linked genetic condition caused by an abnormality in a key enzyme needed for proper function of the immune system. People who have this disorder have low levels of protective antibodies and are vulnerable to repeated and potentially fatal infections.

Description

An integral aspect of the body's ability to resist and fight off infections by microorganisms (bacteria, viruses, parasites, fungi) is the immune system. The immune system is comprised of specialized cells whose function is to recognize organisms that are foreign to the body and destroy them. One set of specialized cells used to fight infection are the B cells. B cells circulate in the bloodstream and produce organism-fighting proteins called antibodies.

Antibodies are made of different classes of immunoglobulin that are produced within a B cell and are then released into the bloodstream, where they attach to invading microorganisms. There are antibodies specifically designed to combine with each and every microorganism, very similar to a lock and key. Once the antibodies attach to the microorganism, it triggers other specialized cells of the immune system to attack and destroy the invader, thus preventing or fighting an existing infection.

In order for antibodies to be produced by the body, the B cells must develop and mature so they are capable of producing the infection-fighting antibodies. When this process does not occur normally, the immune system can not work properly to fight off infection, a state known as immunodeficiency. Bruton agammaglobulinemia (also called X-linked agammaglobulinemia, or congenital agammaglobulinemia) is an inherited immunodeficiency characterized by failure to produce mature B cells and thus to produce the antibodies needed to fight infections. The abnormality in this disorder resides in Bruton tyrosine kinase (BTK, also known as BPK or ATK), an enzyme needed for maturation of B cells. As a result, people with this condition have low levels of mature B cells and the antibodies that they produce, making them vulnerable to frequent and sometimes dangerous infections.

Bruton agammaglobulinemia was the first immunodeficiency disease to be identified, reported by the physician Colonel Ogden C. Bruton in 1952. Bruton's patient, a four-year-old boy, was first admitted to Walter Reed Army Hospital because of an infected knee. The child recovered well when Bruton gave him antibiotics, but over the next four years he had multiple infections. Just at that time, a new instrument was installed in the hospital's laboratory that was able to measure levels of antibodies in the bloodstream. At first the technician believed the machine was defective because it did not detect gammaglobulins (the building blocks of antibodies) in the boy, but Bruton recognized the significance of this finding, and remarked, "Things began to click then. No gammaglobulins; can't build antibodies."

Genetic profile

Bruton agammaglobulinemia is inherited in an X-linked recessive manner; thus, almost all persons with the disorder are male. Females have two X **chromosomes**, which means they have two copies of the BTK

gene, whereas males only have one X chromosome and one copy of the BTK gene. If a male has an altered BTK gene, he will have Bruton agammaglobulinemia. If a female has one altered BTK gene, she will be a carrier and will be at risk to pass the altered gene on to her children. If her son inherits the altered gene, he will be affected; if her daughter inherits the altered gene, she will be a carrier like her mother. Alternatively, if her son or daughter does not inherit the altered gene, they will not be affected and will not pass the altered gene on to their children. Since fathers only pass a Y chromosome to their sons and an X chromosome to their daughters, none of an affected male's sons will develop the disorder but all of the daughters will be carriers.

Mutations in the gene for BTK (located at Xq21.3-22) are responsible for the disease. Over 250 different mutations in BTK have been identified and they are spread almost evenly throughout the BTK gene. While this abnormal gene can be passed from parent to child, in half of the cases a child will show the disease without having a parent with the mutant gene. This is because new alterations in the BTK gene can occur. This new alteration can then be passed on to the affected individual's children.

Demographics

Bruton agammaglobulinemia occurs in all racial groups, with an incidence between one in 50,000 and one in 100,000 individuals.

Signs and symptoms

Bruton agammaglobulinemia is a defect in the B cells, leading to decreased antibodies in the blood and increased vulnerability to infection with certain types of bacteria and a few viruses. Children with Bruton agammaglobulinemia are born healthy and usually begin to show signs of infection in the first three to nine months of life, when antibodies that come from the mother during pregnancy and early breast-feeding disappear. In 20-30% of the cases, however, patients may have slightly higher levels of antibodies present, and symptoms will not appear until later in childhood.

Patients with Bruton agammaglobulinemia can have infections that involve the skin, bone, brain, gastrointestinal tract, sinuses, eyes, ears, nose, airways to the lung, or lung itself. In addition, the bacteria may migrate from the original site of infection and enter the bloodstream, leading to an overwhelming infection of the body that is potentially fatal.

Besides signs of recurrent infections, other physical findings in patients with Bruton agammaglobulinemia include slow growth, wheezing, small tonsils, and abnormal levels of tooth decay. Children may also develop unusual symptoms such as joint disease, destruction of red blood cells, kidney damage, and skin and muscle inflammation. Increased incidence of cancers, such as leukemia, lymphoma, and possibly colon cancer, have

KEY TERMS

Antibiotics—A group of medications that kill or slow the growth of bacteria.

Antibody—A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

B cell—Specialized type of white blood cell that is capable of secreting infection-fighting antibodies.

Bruton tyrosine kinase (BTK)—An enzyme vital for the maturation of B cells.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Immunodeficiency—A defect in the immune system, leaving an individual vulnerable to infection.

Immunoglobulin—A protein molecule formed by mature B cells in response to foreign proteins in the body; the building blocks for antibodies.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Vaccine—An injection, usually derived from a microorganism, that can be injected into an individual to provoke an immune response and prevent future occurrence of an infection by that microorganism.

X chromosome—One of the two sex chromosomes (the other is Y) containing genetic material that, among other things, determine a person's gender.

been associated with Bruton agammaglobulinemia in a small percentage of people.

Infections seen with Bruton agammaglobulinemia are caused by bacteria that are easily destroyed by a normal-functioning immune system. The most common bacterial species responsible for these infections include *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Neisseria meningitides*, *Klebsiella pneumoniae*, *Hemophilus influenzae*, and *Mycoplasma* species. Chronic stomach and intestine infections are often linked to the parasite *Giardia lamblia*.

Patients with Bruton agammaglobulinemia can successfully defend themselves against infection from viruses and fungi because other aspects of the immune system are still functional. However, there are some notable exceptions—people with this disorder are still vulnerable to the hepatitis virus, poliomyelitis virus, and echovirus. Echovirus is particularly troubling, as it can lead to progressive and fatal infections of the brain, joints, and skin.

Diagnosis

Recurrent infections or infections that fail to respond completely or quickly to antibiotics should prompt a diagnostic search for immunodeficiency and Bruton agammaglobulinemia. Another helpful clue to a diagnosis of Bruton agammaglobulinemia is the presence of unusually small lymph nodes and tonsils. Additionally, many patients with this disorder have a history of continuous illness; that is, they do not have periods of well-being between bouts of illness.

When a patient is suspected of having Bruton agammaglobulinemia, the diagnosis is established by several tests. The amount of immunoglobulin is measured in a small amount of blood from the affected individual by a technique called immunoelectrophoresis. In Bruton agammaglobulinemia, all of the immunoglobulins will be markedly reduced or absent. It should be noted that there is some difficulty in diagnosing the disease in a young infant or newborn because immunoglobulins from the mother are still present in the child during the first few months of life.

For those patients in which the exact diagnosis is still unclear, tests can be performed to determine if there has been any response to normal childhood immunizations (such as the tetanus, diptheria, and pertussis vaccines). Patients with Bruton agammaglobulinemia are unable to respond with antibody formation following immunization. Confirmation of the diagnosis can be made by demonstrating abnormally low numbers of mature B cells in the blood or by genetic studies that look for mutations in the BTK gene. When a diagnosis of Bruton agammaglobulinemia is made in a child, **genetic testing** of the BTK gene can be offered to determine if a specific gene change can be identified. If a specific change is identified, carrier testing can be offered to the mother and female relatives. In families where the mother has been identified to be a carrier of a BTK gene change, diagnosis of Bruton agammaglobulinemia before birth is possible, if desired. Prenatal diagnosis is performed on cells obtained by **amniocentesis** (withdrawal of the fluid surrounding a fetus in the womb using a needle) at about 16-18 weeks of pregnancy or from the chorionic villi (a part of the placenta) at 10-12 weeks of pregnancy. In some families, a BTK gene change cannot be identified. Other laboratory techniques may be available to these families such as linkage studies or X chromosome inactivation studies.

Other diagnostic tests have been advocated to track the ongoing health of the patient with Bruton agammaglobulinemia. X rays of the sinuses and chest should be obtained at regular intervals to monitor for the early development of infections and to determine if proper treatment has been established. Lung function tests should also be performed on a regular basis, when the patient is old enough to cooperate. Patients who have ongoing gastrointestinal tract symptoms (diarrhea) should be tested for the parasite *Giardia lamblia*.

Treatment and management

Current research into a cure for Bruton agammaglobulinemia is focusing on the ability of bone marrow transplantation or **gene therapy** to correct the abnormal BTK gene, however, there is no cure at this time. Therefore the goals of treatment are threefold: to treat infection effectively, to prevent repeated infections, and to prevent the lung damage that may result from repeated infections.

The main abnormality in patients with Bruton agammaglobulinemia is a lack of immunoglobulins, which are the building blocks of antibodies. Thus, treatment focuses on replacing immunoglobulin, thereby providing patients with the antibodies they need to fight infection. Immunoglobulin can be obtained from the blood of several donors and given to a patient with Bruton agammaglobulinemia. Treatment with immunoglobulin is given every three to four weeks and is usually effective in preventing infection by various microorganisms.

Side effects from or allergic reactions to immunoglobulin are infrequent, but about 3-12% of people will experience shortness of breath, sweating, increased heart rate, stomach pain, fever, chills, headache, or nausea. These symptoms will usually sub-

side if the immunoglobulin is given slowly, or the reactions may disappear after receiving the immunoglobulin several times. If the reactions continue, it may be necessary to use a special filtering process before giving the immunoglobulin to the patient.

If infection does occur in a patient with Bruton agammaglobulinemia, antibiotics (medications which kill bacteria) are also given to help fight off the infection. Recurrent or chronic infections will develop in some patients despite the use of immunoglobulin. In that case, antibiotics may be given every day, even when there is no infection present, in order to prevent an infection from forming. If chronic diarrhea is experienced by the patient, tests should be performed to look for the parasite *Giardia lamblia*, and proper antibiotics should be given to kill the organism.

Preventative techniques are also very important. Children with Bruton agammaglobulinemia should be treated promptly for even minor cuts and scrapes, and taught to avoid crowds and people with infections. People with this disorder and their family members should not be given vaccinations that contain live organisms (polio, or the measles, mumps, rubella vaccine) as the organism may result in the immunocompromised person contracting the disease that the vaccination is intended to prevent. Referral for **genetic counseling** is appropriate for female relatives seeking information about their carrier status and for family members making reproductive decisions.

Prognosis

Without immunoglobulin treatment, 90% of patients with Bruton agammaglobulinemia will die by the age of eight years old. In most patients who have been diagnosed early and are receiving immunoglobulin on a regular basis, the prognosis is reasonably good. They should be able to lead a relatively normal childhood and need not be isolated to prevent dangerous infections. A full and active lifestyle is to be encouraged.

While current therapy allows most individuals with Bruton agammaglobulinemia to reach adulthood, the prognosis must be guarded. Paralysis of the legs may result from the poliomyelitis virus. Despite what may appear to be adequate immunoglobulin therapy, many patients develop severe, irreversible lung disease. Fatal brain infections have been reported even in patients receiving immunoglobulin therapy, and patients who recover from these infections may be left with severe brain damage. Finally, some patients may develop leukemia or lymphoma.

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ORGANIZATIONS

Immune Deficiency Foundation. 40 W. Chesapeake Ave., Suite 308, Towson, MD 21204. (800) 296-4433. (410) 321-9165. <http://www.primaryimmune.org>.

WEBSITES

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Oren Traub, MD, PhD

Bulldog syndrome *see* **Simpson-Golabi-Behmel syndrome**

C

Campomelic dwarfism *see* **Campomelic dysplasia**

Campomelic dysplasia

Definition

Campomelic dysplasia is a rare, often lethal, genetic condition characterized by multiple abnormalities including short limbs, bowed legs, distinctive facial features, and a narrow chest. It is also often associated with abnormal development of the sex (reproductive) organs in males.

Description

Campomelic dysplasia is also known as campomelic syndrome, campomelic dwarfism, CMD1, and CMPD1. This condition affects the bones and cartilage of the body, causing significantly short arms and legs, bowing of the legs, small chest size, and other skeletal (bony) and non-skeletal problems. Some genetic males with campomelic dysplasia have female sex organs. Death often results in the newborn period due to breathing problems related to the small chest size. Campomelic dysplasia is caused by an alteration (mutation) in a **gene** called SOX9. It usually occurs randomly in a family.

Genetic profile

Campomelic dysplasia is caused by an alteration in the SOX9 gene, which plays a role in bone formation and testes development. Genes are units of hereditary material found on **chromosomes**, which are passed from a parent to a child through the egg and sperm. The information contained in genes is responsible for the development of all the cells and tissues of the body.

The SOX9 gene is located on chromosome 17 (one of the 22 non-sex chromosomes) and it plays a role in both bone formation and testes development. The testes are responsible for producing male hormones. Every developing baby in the womb (fetus), whether genetically male (XY) or female (XX), starts life with the capacity to develop either male or female sex organs. After a few weeks, in an XY fetus, the genitals develop into male genitals if male hormones are present. In the absence of male hormones, a female body type with female genitals results.

In individuals with campomelic dysplasia, the SOX9 gene is altered such that it does not work properly. This causes the testes to form improperly and the male hormones are not produced; thus, individuals who are genetically male (XY) can develop as normal females. This is known as sex-reversal and occurs in about 66% of genetic males with campomelic dysplasia. Since SOX9 is also important for proper bone formation, the bones of the body are also affected causing short stature, bowed legs, and other problems.

There are usually two normal copies of the SOX9 gene: one copy of the gene is inherited from the mother and one copy is inherited from the father. Campomelic dysplasia is inherited as a dominant condition. In dominant conditions, a person only needs one altered gene copy to develop the condition. The alteration in the SOX9 gene that causes campomelic dysplasia is usually random. This means that some unknown event has caused the SOX9 gene (which functions normally in the parent) to become altered in either the sperm of the father or the egg of the mother. When this altered sperm or egg is fertilized, the child that results has campomelic dysplasia. The chance for parents of a child with campomelic dysplasia to have a second child with the same condition is slightly higher than it would be for another couple who has not had a child with this condition. A person who has campomelic dysplasia can pass on their altered SOX9 gene to his or her future children; however, there have not been any reports of individuals with campomelic dysplasia having children.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Dysplasia—The abnormal growth or development of a tissue or organ.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term embryo is used prior to the third month.

Genitals—The internal and external reproductive organs in males and females.

Gonads—The organ that will become either a testis (male reproductive organ) or ovary (female reproductive organ) during fetal development.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Ovary—The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

Testes—The male reproductive organs that produce male reproductive cells (sperm) and male hormones.

Demographics

Campomelic dysplasia is a rare condition that affects males and females of all ethnic groups. It is estimated that approximately one in 10,000 newborns are affected with this condition.

Signs and symptoms

Campomelic dysplasia can affect the body in several ways. Campomelic means "curved limb" and refers to the fact that individuals with campomelic dysplasia typically have curved or bowed legs. Usually there is a dimple in the leg just below the knee. The condition causes significantly short stature, which is evident from birth.

Other features include very small shoulder blades; a very small chest; a curved and twisted spine (kyphoscoliosis); feet that are often turned inwards (clubfeet); dislocated hips; short fingers and toes; and often there are 11 pairs of ribs instead of the usual 12. In some individuals, the pelvic bones and the bones of the spine can also be affected.

A large head size and distinctive facial features such as a high forehead; a flat, small face; small chin; low set ears; and widely spaced eyes are also common. Some individuals have an incomplete closure of the roof of the mouth (cleft palate). Breathing problems are common and are often the cause of death in newborns. The breathing problems usually result from the small chest size, small lungs, and narrow airway passages. Those who survive into early infancy frequently have feeding problems and difficulty breathing.

Individuals with campomelic dysplasia may also have heart defects and hearing loss. Some females with the condition have a Y chromosome. Females with campomelic dysplasia who have a Y chromosome are genetically male; however, their sex organs are female and thus they should be treated as normal females. The intellect of individuals with campomelic dysplasia is usually normal although there have been reports of some individuals who are mentally delayed.

Diagnosis

The diagnosis of campomelic dysplasia is based on the presence of certain clinical features. Some of the bony abnormalities are more obvious on x ray. The features that suggest a diagnosis of campomelic dysplasia include significantly short stature present from birth, small shoulder blades, 11 pairs of ribs instead of 12, small chest size, bowed legs, and a dimple on the leg below the knee.

The diagnosis of campomelic dysplasia can be confirmed through **genetic testing** which requires a blood sample from the affected individual. The genetic test involves identifying the specific alteration in the SOX9 gene. Parents of an affected child may seek testing for campomelic dysplasia in future pregnancies. This can be performed on the developing baby before birth through **amniocentesis** or chorionic villus sampling if an alteration in the SOX9 gene is identified in the previously affected individual. Prenatal testing should only be considered after the gene alteration has been confirmed in

the affected individual and the couple has been counseled regarding the risks of recurrence.

Treatment and management

Campomelic dysplasia is associated with a significant risk for death in the newborn period due to the small chest and small lungs. There is no effective treatment to expand the size of the chest. Those who survive into early infancy have feeding problems and often have difficulty breathing. An occupational therapist may be able to assist with the feeding issues. Breathing problems may necessitate that the child be placed on oxygen.

Some individuals with campomelic dysplasia have significant twisting and bending of their spine (kyphoscoliosis) which can interfere with breathing. A bone specialist (orthopedist) should be consulted for advice on potential treatments such as bracing or surgery. An orthopedist should also be consulted regarding the other bony problems such as **clubfoot** and bowed legs. Individuals with campomelic dysplasia should also have their hearing assessed and their heart examined because of the increased risk for hearing loss and heart defects, respectively.

In females with campomelic dysplasia who have a Y chromosome, the gonads (the organs that will later become either testes or ovaries during fetal development) do not develop properly into ovaries. It is generally recommended that the gonads be surgically removed because there is an increased chance for tumors to occur in the gonads when they do not develop properly.

Very few individuals with campomelic dysplasia live beyond the newborn period but most who do are of normal intelligence. During the school years, it may be necessary to make some changes (such as providing the individual with a step-stool in the bathroom) to foster independence. For some, meeting other individuals of short stature may be beneficial. Groups such as the Little People of America (LPA) serve as a source of information and offer opportunities to meet other people facing similar challenges. Individuals with campomelic dysplasia and their families may benefit from **genetic counseling**, which can provide them with further information on the condition itself and recurrence risks for future pregnancies.

Prognosis

Campomelic dysplasia is associated with a significant risk for death in the newborn period. Most newborns die during the first few hours after birth from breathing problems due to the small chest size and small, underdeveloped lungs. A few individuals with campomelic dysplasia have lived to be adults.

Resources

ORGANIZATIONS

Greenberg Center for Skeletal Dysplasias. 600 North Wolfe St., Blalock 1012C, Baltimore, MD 21287-4922. (410) 614-0977. <http://www.med.jhu.edu/Greenberg.Center/Greenbrg.htm>.

Johns Hopkins University—McKusick Nathans Institute of Genetic Medicine 600 North Wolfe St., Blalock 1008, Baltimore, MD 21287-4922. (410) 955-3071.

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408. (806) 737-8186 or (888) LPA-2001. lpadatabase@juno.com. <http://www.lpaonline.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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"Campomelic Dysplasia." *OMIM—Online Mendelian Inheritance in Man*. <http://www3.ncbi.nlm.nih.gov/>. (March 9, 2001).

Nada Quercia, MS

Campomelic syndrome *see* **Campomelic dysplasia**

Camunati-Englemann disease *see* **Engelmann disease**

Canavan disease

Definition

Canavan disease, which results when the body produces less than normal amounts of a protein called aspartoacylase, is a fatal inherited disorder characterized by progressive damage to the brain and nervous system.

Description

Canavan disease is named after Dr. Myrtelle Canavan who described a patient with the symptoms of Canavan disease but mistakenly diagnosed this patient with Schilder's disease. It was not until 1949, that Canavan disease was recognized as a unique genetic disease by Van Bogaert and Betrand. The credit went to Dr. Canavan, however, whose initial description of the disease dominated the medical literature.

Canavan disease, which is also called aspartoacylase deficiency, spongy degeneration of the brain, and infantile spongy degeneration, results from a deficiency of the enzyme aspartoacylase. This deficiency ultimately results

in progressive damage to the brain and nervous system and causes mental retardation, seizures, tremors, muscle weakness, blindness and an increase in head size. Although most people with Canavan disease die in their teens, some die in childhood and some may live into their twenties and thirties.

Canavan disease is sometimes called spongy degeneration of the brain since it is characterized by a sponginess or swelling of the brain cells and a destruction of the white matter of the brain. Canavan disease is an autosomal recessive genetic condition that is found in all ethnic groups, but is most common in people of Ashkenazi (Eastern European) Jewish descent.

Genetic profile

Canavan disease is an autosomal recessive genetic disease. A person with Canavan disease has changes (mutations) in both of the genes responsible for producing the enzyme aspartoacylase and has inherited one changed **gene** from his or her mother and one changed gene from his or her father. The aspartoacylase gene is called ASPA and is located on chromosome number 17. There are a number of different types of changes in the ASPA gene that can cause Canavan disease, although there are three common gene changes. When the ASPA gene is changed it does not produce any aspartoacylase or produces reduced levels of this enzyme. The amount of aspartoacylase produced depends on the type of gene alteration. Reduced production of aspartoacylase results in lower than normal amounts of this enzyme in the brain and nervous system. Aspartoacylase is responsible for breaking down a substance called N-acetylaspartic acid (NAA). When the body produces decreased levels of aspartoacylase, a build-up of NAA results. This results in the destruction of the white matter of the brain and nervous system and causes the symptoms of Canavan disease.

Parents who have a child with Canavan disease are called carriers, since they each possess one changed ASPA gene and one unchanged ASPA gene. Carriers usually do not have any symptoms since they have one unchanged gene that can produce enough aspartoacylase to prevent the build-up of NAA. Each child born to parents who are both carriers for Canavan disease has a 25% chance of having Canavan disease, a 50% chance of being a carrier and a 25% chance of being neither a carrier nor affected with Canavan disease.

Demographics

Although Canavan disease is found in people of all ethnicities, it is most common in Ashkenazi Jewish individuals. Approximately one in 40 Ashkenazi Jewish individuals are carriers for Canavan disease and approximately one in 6,400 Ashkenazi Jewish people are born with Canavan disease.

Signs and symptoms

Most infants with Canavan disease appear normal for the first month of life. The onset of symptoms, such as a lack of head control and poor muscle tone, usually begins by two to three months of age, although some may have an onset of the disease in later childhood. Children with Canavan disease usually experience sleep disturbances, irritability, and swallowing and feeding difficulties after the first or second year of life. In many cases, irritability resolves by the third year. As the child with Canavan disease grows older there is a deterioration of mental and physical functioning. The speed at which this deterioration occurs will vary for each affected person. Children with Canavan disease are mentally retarded and most will never be able to sit, stand, walk or talk, although they may learn to laugh and smile and reach for objects. People with Canavan disease have increasing difficulties in controlling their muscles. Initially they have poor muscle tone but eventually their muscles become stiff and difficult to move and may exhibit spasms. Canavan disease can cause vision problems and some people with Canavan disease may eventually become blind. People with Canavan disease typically have disproportionately large heads and may experience seizures.

Diagnosis

Diagnostic testing

Canavan disease should be suspected in a person with a large head who has poor muscle control, a lack of head control and a destruction of the white matter of the brain, which can be detected through a computed tomography (CT) scan or magnetic resonance imaging (MRI). A diagnosis of Canavan disease can usually be confirmed by measuring the amount of NAA in a urine sample since a person with Canavan disease typically has greater than five to ten times the normal amount of NAA in their urine. Canavan disease can be less accurately diagnosed by measuring the amount of aspartocylase enzyme present in a sample of skin cells.

Once a biochemical diagnosis of Canavan disease is made, DNA testing may be recommended. Detection of an ASPA gene alteration in a person with Canavan disease can confirm an uncertain diagnosis and help facilitate prenatal diagnosis and carrier testing of relatives. Although there are a number of different ASPA gene changes responsible for Canavan disease, as of 2001, clinical laboratories typically test for only two to three common gene changes. Two of the ASPA gene changes

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid which surrounds a developing baby during pregnancy.

Amniotic sac—Contains the fetus which is surrounded by amniotic fluid.

Biochemical testing—Measuring the amount or activity of a particular enzyme or protein in a sample of blood, urine, or other tissue from the body.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Poor muscle tone—Muscles that are weak and floppy.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

White matter—A substance found in the brain and nervous system that protects nerves and allows messages to be sent to and from the brain to the various parts of the body.

are common in Ashkenazi Jews with Canavan disease and the other ASPA gene change is common in those of other ethnic backgrounds. Testing for other types of changes in the ASPA gene is only done on a research basis.

Carrier testing

DNA testing is the only means of identifying carriers of Canavan disease. If possible, DNA testing should be first performed on the affected family member. If a change in the ASPA gene is detected, then carrier testing can be performed in relatives such as siblings, with an accuracy of greater than 99%. If the affected relative does not possess a detectable ASPA gene change, then carrier testing will be inaccurate and should not be performed. If DNA testing of the affected relative cannot be performed, carrier testing of family members can still be performed but will be less accurate. Carrier testing for the three common ASPA gene mutations identifies approximately 97–99% of Ashkenazi Jewish carriers and 40–55% of carriers of other ethnic backgrounds.

Carrier testing of individuals without a family history of Canavan disease is only recommended for people of Ashkenazi Jewish background since they have a higher risk of being carriers. As of 1998, both the American College of Obstetricians and Gynecologists and the American College of Medical Genetics recommend that DNA testing for Canavan disease be offered to all Ashkenazi Jewish couples who are planning children or who are currently pregnant. If only one member of the couple is of Ashkenazi Jewish background than testing of the Jewish partner should be performed first. If the Jewish partner is a carrier, than testing of the non-Jewish partner is recommended.

Prenatal Testing

Prenatal testing through chorionic villus sampling (CVS) and **amniocentesis** is available to parents who are both carriers for Canavan disease. If both parents possess an ASPA gene change, which is identified through DNA testing, then DNA testing of their baby can be performed. Some parents are known to be carriers for Canavan disease since they already have a child with Canavan disease, yet they do not possess ASPA gene changes that are detectable through DNA testing. Prenatal diagnosis can be performed in these cases by measuring the amount of NAA in the amniotic fluid obtained from an amniocentesis. This type of prenatal testing is less accurate than DNA testing and can lead to misdiagnoses.

Treatment and management

As of 2001, there is no cure for Canavan disease and treatment largely involves the management of symptoms. Seizures and irritability can often be controlled through medication. Children with loss of head control will often benefit from the use of modified seats that can provide full head support. When feeding and swallowing becomes difficult, liquid diets and/or feeding tubes become necessary. Feeding tubes are either inserted through the nose (nasogastric tube) or through a permanent incision in the stomach (gastrostomy). Patients with a later onset and slower progression of the disease may benefit from special education programs and physical therapy. As of 2001, research trials of **gene therapy** are ongoing and involve the transfer of an unchanged ASPA gene into the brain cells of a patient. The goal of gene therapy is to restore normal amounts of aspartoclylase in the brain and nervous system and prevent the build-up of NAA and the symptoms of Canavan disease. The initial results of these early clinical trials have been somewhat promising but it will take time for gene therapy to become a viable treatment for Canavan disease.

Prognosis

The life span and progression of Canavan disease is variable and may be partially dependent on the type of medical care provided and other genetic risk factors. Most people with Canavan disease live into their teens although some die in infancy or survive into their 20's and 30's. There can be a high degree of variability even within families; some families report having one child die in infancy and another die in adulthood. Although different ASPA gene changes are associated with the production of different amounts of enzyme, the severity of the disease does not appear to be related to the type of ASPA gene change. It is, therefore, impossible to predict the lifespan of a particular individual with Canavan disease.

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ORGANIZATIONS

Canavan Foundation. 320 Central Park West, Suite 19D, New York, NY 10025. (212) 877-3945.

Canavan Research Foundation. Fairwood Professional Building, New Fairwood, CT 06812. (203) 746-2436. canavan_research@hotmail.com. <http://www.canavan.org>.

National Foundation for Jewish Genetic Diseases, Inc. 250 Park Ave., Suite 1000, New York, NY 10017. (212) 371-1030. <http://www.nfjgd.org>.

National Tay-Sachs and Allied Diseases Association. 2001 Beacon St., Suite 204, Brighton, MA 02135. (800) 906-8723. ntasd-Boston@worldnet.att.net. <http://www.ntsad.org>.

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Lisa Maria Andres, MS, CGC

Canavan-VanBogaert-Bertrand disease *see* **Canavan disease**

Cancer

Definition

Cancer is not just one disease, but a large group of diseases characterized by uncontrolled and abnormal growth of the cells in the human body and the ability of these cells to spread to distant sites (metastasis). If the spread is not controlled, cancer can result in death.

Description

Cancer, by definition, is a disease of the genes. Genes are formed from deoxyribonucleic acid (**DNA**) and located on **chromosomes**. They carry the hereditary instructions for the cell to make the proteins required for many body functions. Proteins are special chemical compounds that mostly contain carbon, hydrogen, oxygen, and nitrogen. They are required by our bodies to carry out all the processes that allow us to breathe, think, move, etc.

Throughout people's lives, the cells in their bodies are growing, dividing, and replacing themselves. Many genes produce proteins that are involved in controlling the processes of cell growth and division. A change (mutation) occurring in the DNA molecules can disrupt the genes and produce faulty proteins and cells. Abnormal cells can start dividing uncontrollably, eventually forming a new growth known as a "tumor" or "neoplasm" (medical term for cancer meaning "new growth"). In a healthy individual, the immune system can recognize the neoplastic cells and destroy them before they get a chance to divide. However, some abnormal cells may escape immune detection and survive to become cancerous.

Tumors are of two types, benign or malignant. A benign tumor is slow growing and does not spread or invade surrounding tissue. Once the tumor is removed, it usually will not start growing again. A malignant tumor, on the other hand, invades surrounding tissue and can spread to other parts of the body, often very distant from the location of the first tumor. Malignant tumors can be removed, but if the cancer cells have spread too much, the cancer becomes very difficult, if not impossible, to treat.

Most cancers are caused by changes in the cell's DNA that result from exposure to a harmful environment. Environmental factors responsible for causing the initial mutation in the DNA are called carcinogens. Other factors can cause cancer as well. For example, certain hormones have been shown to have an effect on the growth or control of a particular cell line. Hormones are substances made by one organ and passed through the bloodstream to affect the function of other cells in another organ.

While there is scientific evidence that both environmental and genetic factors play a role in most cancers, only 5-10% of all cancers are classified as hereditary. This means that a faulty **gene** which may cause cancer is passed from parent to child. This results in a greater risk for that type of cancer in the offspring of the family. However, if someone has a cancer-related gene, it does not mean they will automatically get cancer. Rather, this person is thought to be "predisposed" to a type of cancer, or more likely to get this cancer when compared to the general population. Various cancers are known to have a hereditary component in some cases. A few examples are **breast cancer**, colon cancer, **ovarian cancer**, skin cancer and **prostate cancer**.

Aside from genes, certain physiological traits that are inherited can contribute to cancers as well. For example, fair skin makes a person more likely to develop skin cancer, but only if they also have prolonged exposure to intensive sunlight.

There are several different types of cancers. Some of the most common types include:

- *Carcinomas* These cancers arise in the epithelium (the layers of cells covering the body's surface and lining the internal organs and various glands). About 80% of human cancers fall into this category. Carcinomas can be subdivided into two subtypes: adenocarcinomas and squamous cell carcinomas. Adenocarcinomas are cancers that develop in an organ or a gland, while squamous cell carcinomas refer to cancers that originate in the skin.
- *Melanomas* This form also originates in the skin, usually in the pigment cells (melanocytes).
- *Sarcomas* These are cancers of the supporting tissues of the body, such as bone, muscle, cartilage, and fat.
- *Leukemias* Cancers of the blood or blood-forming organs.
- *Lymphomas* This type affects the lymphatic system, a network of vessels and nodes that acts as a filter in the body. It distributes nutrients to blood and tissue and prevents bacteria and other foreign substances from entering the bloodstream.
- *Gliomas* Cancers of the nerve tissue.

The most common cancers are skin cancer, lung cancer, colon and rectal (colorectal) cancer, breast cancer (in

women), and prostate cancer (in men). In addition, cancer of the kidneys, ovaries, uterus, pancreas, bladder, and blood and lymph node cancer (leukemias and lymphomas) are also included among the 12 major cancers that affect most Americans.

Genetic profile

Three classes of genes are believed to play roles in the development of cancer. These are:

- Proto-oncogenes. These genes encourage and promote the normal growth and division of cells. When they are defective, they become oncogenes. Oncogenes are overactive proto-oncogenes and they cause excessive cell multiplication that can lead to tumors.
- Tumor suppressor genes. These act as brakes on cell growth. They prevent cells from multiplying uncontrollably. If these genes are defective, there is no control over cell growth and tumors can result.
- DNA repair genes. These genes ensure that each strand of DNA is correctly copied during cell division. When these genes do not function properly, the replicated DNA is likely to have mistakes. This causes defects in other genes and can also lead to tumor formation.

As stated above, approximately 5-10% of cancers have a hereditary component. In these cancers, a child does not inherit cancer from his parents. Rather, he inherits a predisposition to cancer. For example, he may inherit a faulty tumor suppressor gene. This gene is not able to control cell growth but the corresponding gene inherited from the other parent is still functional. Cell growth is then under control. However, as this child grows up, radiation, pollution, or any other harmful environmental factor could change the healthy gene, making it abnormal as well. When both of these tumor suppressor genes are not functioning, a tumor will most likely develop. Defects in proto-oncogenes and DNA repair genes can be inherited as well, leaving a person more vulnerable to cancer than the general population.

Additionally, some cancers seem to be familial. In these cancers, there is not a specific gene that is responsible for the clustering of cancer in a family. However, a particular type of cancer may be seen more often than expected. It is suggested that this is due to a combination of genetic and environmental factors.

Demographics

One out of every four Americans will die from cancer. It is the second leading cause of death in this country, surpassed only by heart disease. Over 1.2 million new cases of cancer are diagnosed every year. The National Cancer Institute estimates that approximately 8.4 million Americans alive in 2001 have a history of cancer. Some of these people have been cured of their cancer while others are still affected with the disease and are undergoing treatment.

Anyone is at risk for developing cancer. Since the occurrence of cancer increases as a person ages, most of the cases are seen in adults who are middle-aged or older. Nearly 80% of cancers are diagnosed in people who are 55 years of age and older.

"Lifetime risk" is the term that cancer researchers use to refer to the probability that an individual will develop cancer over the course of their lifetime. In the United States, men have a one in two lifetime risk of developing cancer, and for women the risk is one in three. Overall, African-Americans are more likely to develop cancer than caucasians. They are also 33% more likely to die of cancer than caucasians.

The major risk factors for cancer are: tobacco, alcohol, diet, sexual and reproductive behavior, infectious agents, family history, occupation, environment, and pollution.

Tobacco

Eighty to ninety percent of the lung cancer cases occur in smokers. Smoking has also been shown to be a contributory factor in cancers of the mouth, pharynx, larynx, esophagus, pancreas, uterine cervix, kidney, and bladder. Smoking accounts for at least 30% of all cancer deaths. Recently, scientists have also shown that secondhand smoke (or passive smoking) can increase one's risk of developing cancer.

Alcohol

Excessive consumption of alcohol is a risk factor in some cancers, such as **liver cancer** and breast cancer. Alcohol, in combination with tobacco, significantly increases the chances that an individual will develop mouth, pharynx, larynx, and esophageal cancers. The combined effect of tobacco and alcohol is greater than the sum of their individual effects.

Diet and physical activity

One-third of all cancer deaths are due to a poor adult diet. High-fat diets have been associated with cancers of the colon and rectum, prostate, endometrium, and possibly breast. Consumption of meat, especially red meat, has been associated with increased cancer at various sites, such as the colon and prostate. Additionally, a high calorie diet and low level of physical activity can lead to obesity. This increases the risk for cancer at various sites including the breast, colon and rectum, prostate, kidney, and endometrium.

Sexual and reproductive behavior

The human papilloma virus, which is a sexually transmitted disease, has been shown to cause cancer of the cervix. Having many sexual partners and becoming sexually active early has been shown to increase a woman's chances of contracting this disease and, therefore, developing cervical cancer. In addition, it has also been shown that women who do not bear any children or those who become pregnant late in life have an increased risk for both ovarian and breast cancer.

Hormone replacement therapy

As women go through menopause, a doctor may recommend hormone replacement therapy. This involves taking female hormones (called estrogen and progesterone) to control certain symptoms that occur during this time of a woman's life, such as hot flashes and vaginal dryness. Taking estrogen alone can increase the risk for uterine cancer. However, progesterone is often prescribed at the same time to counteract the cancerous effects of estrogen. There is a questionable relationship between hormone replacement therapy and breast cancer as well. As of 2001, this relationship is not fully understood.

Family history

Some types of cancers tend to occur more frequently among members of a family. In most cases, this happens by chance or due to common family habits such as cigarette smoking or excessive sun exposure. However, this can also be due to a genetic predisposition that is passed from generation to generation. For example, if a certain gene called BRCA1 is defective in a given family, members of that family may have an increased risk to develop breast, colon, ovarian and prostate cancer. Other defective genes have been identified that can make a person susceptible to various types of cancer. Therefore, inheriting particular genes can increase a person's chance to develop cancer.

Occupational hazards

There is strong evidence proving that occupational hazards account for 4% of all cancer deaths. For example, asbestos workers have an increased incidence of lung cancer. Similarly, bladder cancer is associated with dye, rubber, and gas workers; skin and lung cancer with smelters, gold miners and arsenic workers; leukemia with glue and varnish workers; liver cancer with PVC manufacturers; and lung, bone, and bone marrow cancer with radiologists and uranium miners.

Environment

High-frequency radiation has been shown to cause human cancer. Ultra-violet radiation from the sun accounts for a majority of melanoma. Other sources of radiation are x rays, radioactive substances, and rays that enter the Earth's atmosphere from outer space. Virtually any part of the body can be affected by these types of radiation, especially the bone marrow and the thyroid gland.

Additionally, being exposed to substances such as certain chemicals, metals, or pesticides can increase the risk of cancer. Asbestos is an example of a well-known carcinogen. It increases the risk for lung cancer. This risk is increased even further for a smoker who is exposed to asbestos over a period of time.

Signs and symptoms

Almost every tissue of the body can give rise to abnormal cells that cause cancer and each of these cancers is very different in symptoms and prognosis.

Cancer is also a progressive disease and goes through several stages. Each stage can produce a number of symptoms. Unfortunately, many types of cancer do not display any obvious symptoms or cause pain until the disease has progressed to an advanced stage. Early signs of cancer are often subtle and are easily mistaken for signs of other less-dangerous diseases.

Despite the fact that there are several hundred different types of cancers producing very different symptoms, the American Cancer Society has established the following seven symptoms as possible warning signs of cancer:

- Changes in the size, color, or shape of a wart or a mole
- A sore that does not heal
- Persistent cough, hoarseness, or sore throat
- A lump or thickening in the breast or elsewhere
- Unusual bleeding or discharge
- Chronic indigestion or difficulty in swallowing
- Any change in bowel or bladder habits

Many other diseases can produce similar symptoms. However, it is important to have these symptoms checked as soon as possible, especially if they do not stop. The earlier a cancer is diagnosed and treated, the better the chance of a cure. Many cancers, such as breast cancer, may not have any early symptoms. Therefore, it is important to undergo routine screening tests, such as breast self-exams and mammograms.

Diagnosis

If a person has symptoms of cancer, the doctor will begin with a complete medical history and a thorough physical examination. Different parts of the body will be examined to identify any variations from the normal size,

KEY TERMS (CONTINUED)

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

Mammogram—A procedure in which both breasts are compressed/flattened and exposed to low doses of x rays, in an attempt to visualize the inner breast tissue.

Maori—A native New Zealand ethnic group.

Medulloblastoma—Tumor of the central nervous system derived from undifferentiated cells of the primitive medullary tube.

Melanoma—Tumor, usually of the skin.

Metachronous—Occurring at separate time intervals.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Metastatic cancer—A cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.

Multifocal breast cancer—Multiple primary cancers in the same breast.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nitrates/nitrites—Chemical compounds found in certain foods and water that, when consumed, may increase the risk of gastric cancer.

Osteoma—A benign bone tumor.

Palliative—Treatment done for relief of symptoms rather than a cure.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Pancreatitis—Inflammation of the pancreas.

Pelvic examination—Physical examination performed by a physician, often associated with a Pap smear. The physician inserts his/her finger into a woman's vagina, attempting to feel the ovaries directly.

Pernicious anemia—A blood condition with decreased numbers of red blood cells related to poor vitamin B_{12} absorption.

Peutz-Jeghers syndrome (PJS)—Inherited syndrome causing polyps of the digestive tract and spots on the mouth as well as increased risk of cancer.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Primary cancer—The first or original cancer site, before any metastasis.

Prophylactic—Preventing disease.

(continued)

feel, and texture of the organ or tissue. Additionally, the doctor may order various other tests.

Laboratory tests on blood and urine are often used to obtain information about a person's health. If cancer is suspected, a special test can be done that measures the amount of certain substances, called tumor markers, in the blood, urine, or particular tissues. These proteins are released from some types of cancer cells. Thus, the levels of these substances may be abnormal when certain cancers are present. However, laboratory tests alone cannot be used to make a definitive diagnosis of cancer. Blood tests are generally more useful in monitoring the effectiveness of the treatment or in following the course of the disease and detecting any signs of recurrence.

The doctor may also look for tumors by examining pictures of areas inside the body. The most common way to obtain these images is by using x rays. Other techniques used to obtain pictures of the inside of the body include computed tomography scanning (CT scan), magnetic resonance imaging (MRI), and ultrasonography.

The most definitive diagnostic test is the biopsy. In this technique, a piece of tissue is surgically removed for examination under a microscope. A biopsy provides information about the cellular nature of the abnormality, the stage it has reached, the aggressiveness of the cancer, and the extent of its spread. Further analysis of the tissue obtained by biopsy defines the cause of the abnormality. Since a biopsy provides the most accurate analysis, it is considered the gold standard of diagnostic tests for cancer.

Regular screening examinations conducted by healthcare professionals can result in the early detection of various types of cancer. If detected at an early stage, treatment is more likely to be successful. For example, the American Cancer Society recommends an annual

KEY TERMS (CONTINUED)

Prostatectomy—The surgical removal of the prostate gland.

Proximal—Near the point of origin.

Radiation—High energy rays used in cancer treatment to kill or shrink cancer cells.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Rectum—The end portion of the intestine that leads to the anus.

Semen—A whitish, opaque fluid released at ejaculation that contains sperm.

Seminal vesicles—The pouches above the prostate that store semen.

Sore—An open wound or a bruise or lesion on the skin.

Staging—A method of describing the degree and location of cancer.

Stomach—An organ that holds and begins digestion of food.

Synchronous—Occurring simultaneously.

Testicles—Two egg-shaped glands that produce sperm and sex hormones.

Testosterone—Hormone produced in the testicles that is involved in male secondary sex characteristics.

Trans-rectal ultrasound—A procedure where a probe is placed in the rectum. High-frequency sound waves that cannot be heard by humans are sent out from the probe and reflected by the prostate. These sound waves produce a pattern of echoes that are then used by the computer to create sonograms or pictures of areas inside the body.

Transvaginal ultrasound—A way to view the ovaries using sound waves. A probe is inserted into the vagina and the ovaries can be seen. Color doppler imaging measures the amount of blood flow, as tumors sometimes have high levels of blood flow.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Whipple procedure—Surgical removal of the pancreas and surrounding areas including a portion of the small intestine, the duodenum.

X ray—An image of the body made by the passing of radiation through the body.

X rays—High energy radiation used in high doses, either to diagnose or treat disease.

mammogram (x ray of the breast) for women over the age of 40 to screen for breast cancer. It also recommends a sigmoidoscopy (procedure using a thin, lighted tube to view the inside of the colon) every five years for people over the age of 50. This technique can check for colorectal cancer. Self-examinations for cancers of the breast, testes, mouth and skin can also help in detecting tumors.

Recent progress in molecular biology and cancer genetics have led to the development of several tests designed to assess one's risk of developing certain types of cancer. This **genetic testing** involves looking closely at certain genes that have been linked to particular cancers. If these genes are abnormal, a person's risk for certain types of cancer increases. At present, there are many limitations to genetic testing. The tests may be uninformative and they are useful to a very small number of people. Additionally, there are concerns about insurance coverage and employment discrimination for someone who has an increased risk for cancer. As of 2001, these tests are reserved only for very specific people. A hereditary cancer clinic can help to assess who may benefit from this type of testing.

Treatment

The aim of cancer treatment is to remove all or as much of the tumor as possible and to prevent the metastasis of the primary tumor. While devising a treatment plan for cancer, the likelihood of curing the cancer must be weighed against the side effects of the treatment. For example, if the cancer is very aggressive and a cure is not possible, then the treatment should be aimed at relieving the symptoms and controlling the cancer for as long as possible.

Cancer treatment can take many different forms and it is always tailored to the individual patient. The decision on which type of treatment to use depends on the type and location of cancer and the extent to which it has already spread. The doctor will also consider the patient's age, sex, general health status, and personal

TABLE 1

Childhood cancers associated with congenital syndromes or malformations

Syndrome or Anomaly	Tumour
Aniridia	Wilms tumor
Hemihypertrophy	Wilms tumor, hepatoblastoma, adrenocortical carcinoma
Genito-urinary abnormalities (including testicle maldescent)	Wilms tumor, Ewing sarcoma, nephroblastoma, testicular carcinoma
Beckwith-Wiedmann syndrome	Wilms tumor, neuroblastoma, adrenocortical carcinoma
Dysplastic naevus syndrome	Melanoma
Nevoid basal cell carcinoma syndrome	Basal cell carcinoma, medulloblastoma, rhabdomyosarcoma
Poland syndrome	Leukemia
Trisomy-21 (Down syndrome)	Leukemia, retinoblastoma
Bloom syndrome	Leukemia, gastrointestinal carcinoma
Severe combined immune deficiency disease	EBV-associated B-lymphocyte lymphoma/leukemia
Wiscott-Aldridge syndrome	EBV-associated B-lymphocyte lymphoma
Ataxia telangiectasia	EBV-associated B-lymphocyte lymphoma, gastric carcinoma
Retinoblastoma	Wilms tumor, osteosarcoma, Ewing sarcoma
Fanconi anemia	Leukemia, squamous cell carcinoma
Multiple endocrine neoplasia syndromes (MEN I, II, III)	Adenomas of islet cells, pituitary, parathyroids, and adrenal glands Submucosal neuromas of the tongue, lips, eyelids Pheochromocytomas, medullary carcinoma of the thyroid, malignant schwannoma, non-appendiceal carcinoid
Neurofibromatosis (von Recklinghausen syndrome)	Rhabdomyosarcoma, fibrosarcoma, pheochromocytomas, optic glioma, meningioma

treatment preferences. Treatment can be local, meaning that it seeks to destroy cancer cells in the tumor and the surrounding area. It can also be systemic, meaning that the treatment drugs will travel through the bloodstream and reach cancer cells all over the body. Surgery and radiation are local treatments. Chemotherapy, immunotherapy, and hormone therapy are examples of systemic treatments.

Surgery

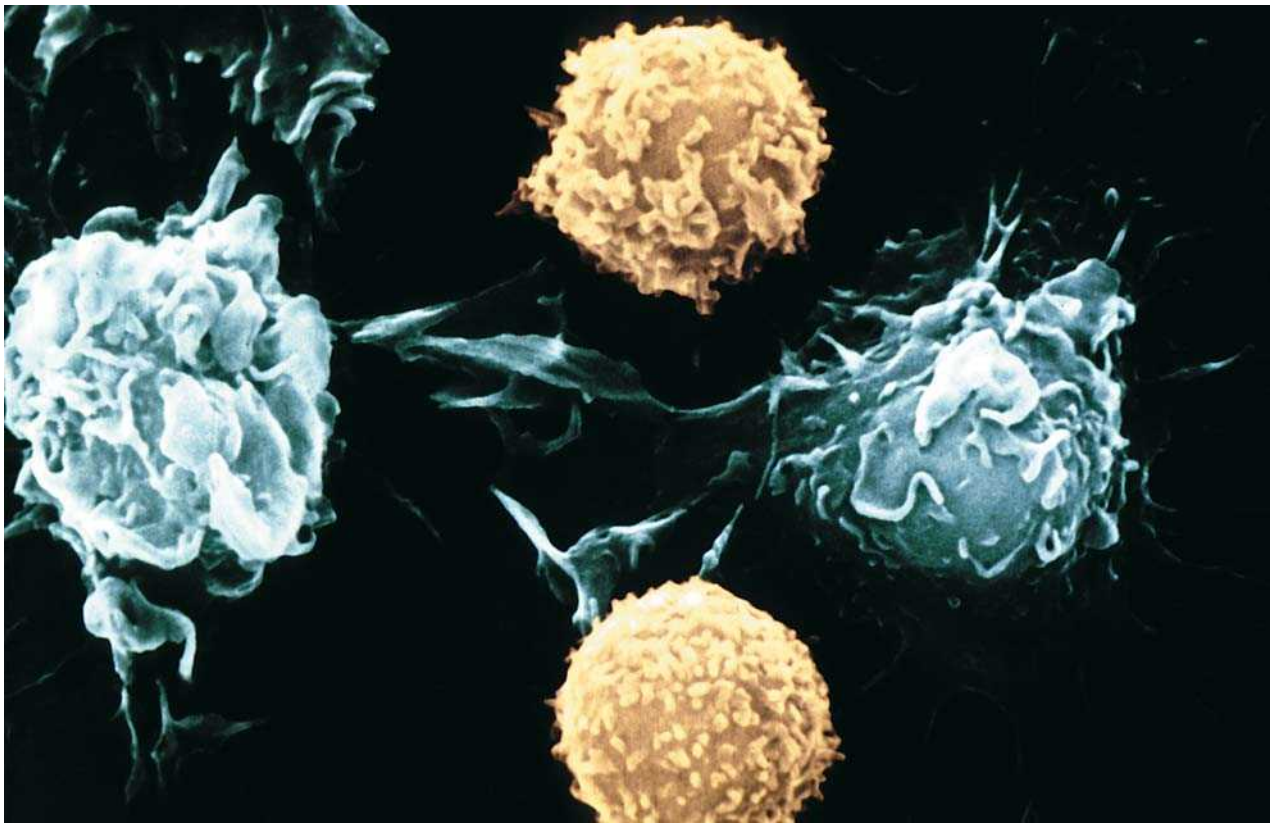
Surgery can be used for many purposes in cancer therapy.

- Treatment surgery: This involves removal of the tumor to cure the disease. It is typically performed when the cancer is localized to a discrete area. Along with the cancer, some of the surrounding tissue may also be removed to ensure that no cancer cells remain in the area. Since cancer usually spreads via the lymphatic system, lymph nodes that are near the tumor site may be examined and removed as well.
- Preventive surgery: Preventive or prophylactic surgery involves removal of an abnormal area that is likely to become malignant over time. For example, 40% of people with a colon disease, called ulcerative colitis, ultimately die of colon cancer. Rather than live with the fear of developing colon cancer, these people may choose to have their colons removed in order to reduce their risk of cancer.
- Diagnostic purposes: The most definitive tool for diagnosing cancer is a biopsy. Sometimes a biopsy can be performed by inserting a needle through the skin. In other cases, the only way to obtain a tissue sample for biopsy is by performing a surgical operation.
- Cytoreductive surgery: This is a procedure in which the doctor removes as much of the cancer as possible. He then treats the remaining cancer cells with radiation therapy, chemotherapy, or both.
- Palliative surgery: This type of surgery is aimed at relieving cancer symptoms or slowing the progression of disease. It is not designed to cure the cancer. For example, if the tumor is very large or has spread to many places in the body, removing the entire tumor may not be an option. However, by decreasing the size of the tumor, pain may be alleviated. This is known as "debulking surgery."

Radiation therapy

Radiation uses high-energy rays to kill cancer cells. This treatment may be used instead of surgery. It also may be used before surgery to shrink a tumor or after surgery to destroy any remaining cancer cells.

Radiation can be either external or internal. In the external form, the radiation comes from a machine that aims the rays at the tumor. In internal radiation (also known as brachytherapy), radioactive material is sealed in needles, seeds, or wires and placed directly in or near the tumor. Radiation may lead to various side effects, such as fatigue, hair loss, and a susceptibility to infections. However, these side effects can usually be controlled.



A scanning electron micrograph (SEM) of cancer cells. *(Photo Researchers, Inc.)*

Chemotherapy

Chemotherapy is the use of drugs to kill cancer cells. The anticancer drugs are usually released into the entire body (systemic therapy) so as to destroy the hard-to-detect cancer cells that have spread and are circulating in the body. Chemotherapy is based on the principle that cancer cells are affected more dramatically than the normal cells because they are rapidly dividing. Chemotherapeutic drugs can be injected into a vein, the muscle, or the skin or they may be taken by mouth.

When chemotherapy is used before surgery, it is known as primary chemotherapy or "neoadjuvant chemotherapy." Its purpose is usually to reduce the size of the tumor. The more common use of chemotherapy is in "adjuvant therapy." In this form of treatment, chemotherapy is given after surgery to destroy any remaining cancer cells and to help prevent cancer from recurring. Chemotherapy can also be used in conjunction with radiation therapy.

The side effects of chemotherapy vary but can include susceptibility to infections, fatigue, poor appetite, weight loss, nausea, diarrhea, and hair loss. Decreased fertility can be a long-term side effect in some patients who undergo chemotherapy.

Immunotherapy

Immunotherapy, also called biological therapy, is the use of treatments that promote or support the body's immune system response to cancer. The side effects of this immunotherapy are variable but include flu-like symptoms, weakness, loss of appetite, and skin rash. These symptoms will subside after the treatment is completed.

Bone marrow failure is a complication of chemotherapy. When high dose chemotherapy is used, this failure is anticipated. Bone marrow transplantation (BMT) or peripheral stem cell transplantation (PSCT) are techniques used to treat this complication. Both techniques provide healthy stem cells for the patient. Stem cells are immature cells that mature into blood cells. They can replace the patient's own stem cells that have been damaged or destroyed by chemotherapy or radiation. It allows a patient to undergo very aggressive treatment for their cancer. Patients who receive BMT or PSCT have an increased risk of infection, bleeding, and other side effects due to the chemotherapy and radiation. Graft-versus-host disease may also occur as well. This complication occurs when the donated marrow reacts against a patient's tissues. It can occur any time after the trans-

plant. Drugs may be given to reduce the risk of graft-versus-host disease and to treat the problem if it occurs.

Hormone therapy

Hormone therapy is used to fight certain cancers that depend on hormones for their growth. Drugs can be used to block the production of hormones or change the way they work. Additionally, organs that produce hormones may be removed. As a result of this therapy, the growth of the tumor slows and survival may be extended for several months or years.

Alternative and complementary therapies

There are certain cancer therapies that have not been scientifically tested and approved. If these unproven treatments are used instead of the standard therapy, this is known as "alternative therapy." If used along with standard therapy, this is known as "complementary therapy." The use of alternative therapies must be carefully considered because some of these unproven treatments may have life-threatening side effects. Additionally, if someone uses alternative therapy, they may lose the opportunity to benefit from the standard, proven therapy. However, some complementary therapies may help to relieve symptoms of cancer, decrease the magnitude of side effects from treatment, or improve a patient's sense of well-being. The American Cancer Society recommends that anyone considering alternative or complementary therapy consult a health care team.

Prevention

According to experts from leading universities in the United States, a person can reduce the chances of getting cancer by following these guidelines:

- Eating plenty of fruits and vegetables
- Exercising vigorously for at least 20 minutes every day
- Avoiding excessive weight gain
- Avoiding tobacco (including second hand smoke)
- Decreasing or avoiding consumption of animal fats and red meats
- Avoiding excessive amounts of alcohol
- Avoiding the midday sun (between 11 a.m. and 3 p.m.) when the sun's rays are the strongest
- Avoiding risky sexual practices
- Avoiding known carcinogens in the environment or work place

Certain drugs that are currently being used for treatment can also be suitable for prevention. For example, the drug tamoxifen, also called Nolvadex, has been very effective against breast cancer and is now thought to be helpful in the prevention of breast cancer. Similarly, retinoids derived from vitamin A are being tested for their ability to slow the progression or prevent head and neck cancers.

Prognosis

Most cancers are curable if detected and treated at their early stages. A cancer patient's prognosis is affected by many factors, particularly the type of cancer the patient has, the stage of the cancer, the extent to which it has metastasized and the aggressiveness of the cancer. In addition, the patient's age, general health status and the effectiveness of the treatment being pursued are also important factors.

To help predict the future outcome of cancer and the likelihood of recovery from the disease, five-year survival rates are used. The five-year survival rate for all cancers combined is 59%. This means that 59% of people with cancer are expected to be alive five years after they are diagnosed. These people may be free of cancer or they may be undergoing treatment. It is important to note that while this statistic can give some information about the average survival of cancer patients in a given population, it cannot be used to predict individual prognosis. No two patients are exactly alike. For example, the five-year survival rate does not account for differences in detection methods, types of treatments, additional illnesses, and behaviors.

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"What You Need to Know about Cancer." *Scientific American* 275, no. 3 (September 1996).

ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

American Foundation for Urologic Disease, Inc. 1128 North Charles St., Baltimore, MD 21201-5559. (410)468-1808. <http://www.afud.org>.

American Liver Foundation. 75 Maiden Lane, Suite 603, New York, NY 10038. (800) 465-4837 or (888) 443-7222. <http://www.liverfoundation.org>.

National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda, MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

National Familial Pancreas Tumor Registry. Johns Hopkins Hospital, Weinberg Building, Room 2242, 401 North Broadway, Baltimore, MD 21231-2410. (410) 955-9132. <http://www.path.jhu.edu/pancreas>.

University of Texas M.D. Anderson Cancer Center. 1515 Holcombe Blvd., Houston, TX 77030. (800) 392-1611. <http://www.mdanderson.org>.

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American Cancer Society. *Cancer Resource Center.* <http://www3.cancer.org/cancerinfo/>.

National Cancer Institute. *CancerNet.* <http://cancernet.nci.nih.gov>.

University of Pennsylvania Cancer Center. *Oncolink.* <http://cancer.med.upenn.edu>.

Mary E. Freivogel, MS

Cardiofaciocutaneous syndrome

Definition

Cardiofaciocutaneous syndrome is an extremely rare genetic condition present at birth and characterized by mental retardation, slow growth, and abnormalities of the heart, face, skin, and hair. There is no cure for cardiofaciocutaneous syndrome. Treatment centers on the correction of heart abnormalities and strategies to improve the quality of life of the affected individual.

Description

Cardiofaciocutaneous syndrome was first identified and described in 1986 by J. F. Reynolds and colleagues at the Shodair Children's Hospital in Helena, Montana and at the University of Utah. These physicians identified and described eight children with a characteristic set of mental and physical changes including abnormal skin conditions, an unusual face, sparse and curly hair, heart defects, and mental retardation. These physicians named the syndrome based on the changes of the heart (cardio), face (facio), and skin (cutaneous). Since that time, physicians have used the descriptions originally put forth by Dr. Reynolds to identify other children with cardiofaciocutaneous syndrome.

Scientific research conducted over the past decade suggests that cardiofaciocutaneous syndrome is associated with a change in the genetic material. However, it is still not known precisely how this change in the genetic material alters growth and development in the womb to cause cardiofaciocutaneous syndrome.

Cardiofaciocutaneous syndrome can sometimes be confused with another genetic syndrome, **Noonan syndrome**. Children with Noonan syndrome have abnormalities in the same genetic material as those with cardiofaciocutaneous syndrome, and the two syndromes share some similar physical characteristics. Many scientists believe that the two diseases are different entities and should be regarded as separate conditions, while others believe that Noonan syndrome and cardiofaciocutaneous syndrome may be variations of the same disease.

Genetic profile

Recent research has shown that people with cardiofaciocutaneous syndrome have changes in a **gene** located on a region of human chromosome 12 (locus 12q24), but the precise gene and genetic alteration is unknown.

In almost all cases of cardiofaciocutaneous syndrome, there is no family history of the disease. These cases are thought to represent new genetic changes that occur randomly and with no apparent cause and are termed sporadic. While the cause of the genetic change is still unclear, some studies suggest that the age of the father might be important in the genesis of the disease. In 20 cases for which information was available, scientists noted that fathers of affected children tended to be older (average age of 39 years) when the child was conceived. Therefore, it is believed that a change in the genetic material of the father's sperm may occur as the man ages, and that he may, in turn, pass this genetic change to the child, resulting in cardiofaciocutaneous syndrome.

Only one abnormal gene in a gene pair is necessary to display the disease. This is an example of a dominant gene (i.e. the abnormal gene of the gene pair dominates over the normal gene, resulting in the syndrome).

Demographics

Cardiofaciocutaneous syndrome is an extremely rare condition. Because the syndrome is relatively new and only a small number of physicians have actual first-hand experience with the diagnosis of the syndrome, some children with the syndrome may not be diagnosed, particularly if they are living in areas where sophisticated medical care is not available. As a result, it is difficult to know how many children are affected by cardiofaciocu-

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Bitemporal constriction—Abnormal narrowing of both sides of the forehead.

Macrocephaly—A head that is larger than normal.

Noonan syndrome—A genetic syndrome that possesses some characteristics similar to cardiofaciocutanous syndrome. It is unclear whether the two syndromes are different or two manifestations of the same disorder.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

taneous syndrome. However, scientists estimate that less than 200 children worldwide are presently affected by this condition.

Because the syndrome is so rare, it is not known whether the disease is distributed equally among different geographic areas or whether different ethnic groups have higher incidences of the syndrome.

Signs and symptoms

Individuals with cardiofaciocutaneous syndrome have distinct malformations of the head and face. An unusually large head (macrocephaly), a prominent forehead, and abnormal narrowing of both sides of the forehead (bitemporal constriction) are typical. A short, upturned nose with a low nasal bridge and prominent external ears that are abnormally rotated toward the back of the head are also seen. In most cases, affected individuals have downward slanting eyelid folds, widely spaced eyes, drooping of the upper eyelids, inward deviation of the eyes, and other eye abnormalities. In addition to having unusually dry, brittle, curly scalp hair, affected individuals may lack eyebrows and eyelashes.

Individuals with cardiofaciocutaneous syndrome may also have a range of skin abnormalities, varying from areas of skin inflammation to unusually dry, thickened, scaly skin over the entire body. Most affected individuals also have **congenital heart defects**, particularly obstruction of the normal flow of blood from the right chamber of the heart to the lungs and/or an abnormal opening in the wall that separates two of the heart chambers.

In addition, most individuals with the disorder experience growth delays, mild to severe mental retardation, and abnormal delays in the acquisition of skills requiring the coordination of muscular and mental activity. Other abnormalities encountered in children with cardiofaciocutaneous syndrome include seizures, abnormal movements of the eye, poor muscle tone, and poor digestion. In some cases, additional abnormalities may be present.

Diagnosis

The diagnosis of cardiofaciocutaneous syndrome relies on physical exam by a physician familiar with the condition and by radiographic evaluation, such as the use of x rays or ultrasound to define abnormal or missing structures that are consistent with the criteria for the condition (as described above). Although a diagnosis may be made as a newborn, most often the features do not become fully evident until early childhood.

There is no laboratory blood test or commercially available genetic test that can be used to identify people with cardiofaciocutaneous syndrome. However, because the condition is so rare, advanced genetic analysis may be available as part of a research study to determine if changes in regions of chromosome 12 are present.

Cardiofaciocutaneous syndrome can be differentiated from Noonan syndrome by the presence of nervous system abnormalities, such as low muscle tone, seizures, and abnormal movements of the eye, as well as by typical changes in the hair and skin.

Treatment and management

There is no cure for cardiofaciocutaneous syndrome. The genetic change responsible for cardiofaciocutaneous syndrome is present in every cell of the body and, at the current time, there is no means of correcting this genetic abnormality.

Treatment of the syndrome is variable and centers on correcting the different manifestations of the condition. For children with heart defects, surgical repair is often necessary. This may take place shortly after birth if the heart abnormality is life threatening, but often physicians will prefer to attempt a repair once the child has grown older and the heart is more mature. For children who experience seizures, lifelong treatment with anti-seizure medications is often necessary. Oral or topical medications may also be used to treat the inflammatory skin conditions and provide some symptomatic and cosmetic relief.

During early development and progressing into young adulthood, children with cardiofaciocutaneous should be educated and trained in behavioral and mechanical methods to adapt to their disabilities. This program is usually initiated and overseen by a team of

health care professionals including a pediatrician, physical therapist, and occupational therapist. A counselor specially trained to deal with issues of disabilities in children is often helpful is assessing problem areas and encouraging healthy development of self-esteem. Support groups and community organizations for people with cardiofaciocutaneous syndrome or other disabilities often prove useful to the affected individual and their families. Specially-equipped schools or enrichment programs should also be sought.

Children with cardiofaciocutaneous syndrome should be seen regularly by a team of health care professionals, including a pediatrician, medical geneticist, pediatric cardiologist, dermatologist, and neurologist. Consultation with a reconstructive surgeon may be of use if some of the physical abnormalities are particularly debilitating.

Prognosis

The prognosis of children with cardiofaciocutaneous syndrome depends on the severity of the symptoms and the extent to which appropriate treatments are available. In addition to the physical disabilities, the mental retardation and other nervous system effects can be severe. Since cardiofaciocutaneous syndrome was discovered relatively recently, very little is known regarding the level of functioning and the average life span of individuals affected with the condition.

Resources

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Neri G., and J. M. Opitz. "Heterogeneity of cardio-facio-cutaneous syndrome." *American Journal of Medical Genetics* 95 (November 2000): 135–43.

ORGANIZATIONS

Cardio-Facio-Cutaneous Syndrome Foundation. 3962 Van Dyke St., White Bear Lake, MN 55110. <http://www.cfcfoundation.com>.

CardioFacioCutaneous Support Network. 157 Alder Ave., McKee City, NJ 08232. (609) 646-5606.

Cardiofaciocutaneous Syndrome Family Network. 183 Brown Rd., Vestal, NY 13850. (607) 772-9666. <http://www.cfcsyndrome.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

"Cardiofaciocutaneous syndrome." *OMIM—Online Mendelian Inheritance in Man.* National Center for Biotechnology Information. <http://www3.ncbi.nlm.nih.gov/htbin-post/Omim>.

Oren Traub, MD, PhD

Carnitine palmitoyltransferase deficiency

Definition

Carnitine palmitoyltransferase (CPT) deficiency refers to two separate, hereditary diseases of lipid metabolism, CPT-I deficiency and CPT-II deficiency. CPT-I deficiency affects lipid metabolism in the liver, with serious physical symptoms including coma and seizures. Two types of CPT-II deficiency are similar in age of onset and type of symptoms to CPT-I deficiency. The third, most common type of CPT-II deficiency involves intermittent muscle disease in adults, with a potential for myoglobinuria, a serious complication affecting the kidneys. Preventive measures and treatments are available for CPT-I deficiency, and the muscle form of CPT-II deficiency.

Description

Carnitine palmitoyltransferase (CPT) is an important enzyme required by the body to use (metabolize) lipids (fats). CPT speeds up the transport of long-chain fatty acids across the inner mitochondria membrane. This transport also depends on carnitine, also called vitamin B_7.

Until the 1990s, discussion centered on whether defects in a single CPT enzyme were responsible for all the conditions resulting from CPT deficiency. Careful chemical and genetic analysis eventually pointed to two different enzymes: CPT-I and CPT-II. Both CPT-I and CPT-II were shown to play an important role in the metabolism of lipids. CPT deficiency of any type affects the muscles, so these disorders are considered to be metabolic myopathies (muscle diseases), or more specifically, mitochondrial myopathies, meaning myopathies that result from abnormal changes occurring in the mitochondria of the cells as a result of excessive lipid build-up.

Understanding the symptoms of CPT requires some familiarity with the basics of lipid metabolism in muscle cells. Fatty acids (FA) are the major component of lipids. FAs contain a chain of carbon atoms of varying length.

Long-chain fatty acids (LCFAs) are the most abundant type, and have at least 12 carbon atoms. Lipids and glucose (sugar) are the primary sources of energy for the body. Both are converted into energy (oxidized) inside mitochondria, structures within each cell where numerous energy-producing chemical reactions take place. Each cell contains many mitochondria.

A single mitochondrion is enclosed by a double-layer membrane. LCFAs are unable to pass through the inner portion of this membrane without first being bound to carnitine, a type of amino acid. CPT-I chemically binds carnitine to LCFAs, allowing transfer through the inner membrane. However, LCFAs cannot be oxidized inside the mitochondrion while still attached to carnitine, so CPT-II reverses the action of CPT-I and removes carnitine. Once accomplished, LCFAs can proceed to be metabolized. Therefore, deficiency of either CPT-I or CPT-II results in defective transfer and utilization of LCFAs in the mitochondria.

CPT-I is involved in lipid metabolism in several tissues, most importantly the liver. There, LCFAs are broken down and ketone bodies are produced. Like lipids and glucose, ketone bodies are used by the body as fuel, especially in the brain and muscles. Deficiency of CPT-I in the liver results in decreased levels of ketone bodies (hypoketosis), as well as low blood-sugar levels (hypoglycemia). Hypoketosis combined with hypoglycemia in a child can lead to weakness, seizures, and coma. Symptoms can be reversed by glucose infusions, as well as supplementation with medium-chain fatty acids, which do not require CPT-I to produce energy.

As noted, glucose and fatty acids are important energy sources for the body. During exercise, the muscles initially use glucose as their primary fuel. After some time, however, glucose is depleted and the muscles switch to using fatty acids by a chemical process called oxidation. CPT-II deficiency results in a decrease in LCFAs that can be used by the mitochondria, and the muscles eventually exhaust their energy supply. This explains why prolonged exercise may cause an attack of muscle fatigue, stiffness, and pain in people with CPT-II deficiency. The ability to exercise for short periods is not affected. Infections, stress, muscle trauma, and exposure to cold also put extra demands on the muscles and can trigger an attack. Fasting, or a diet high in fats and low in carbohydrates (complex sugars), deplete glucose reserves in the muscles and are risk factors as well.

In some cases, CPT deficiency results in the breakdown of muscle tissue, a process called rhabdomyolysis, and it causes some components of muscle cells to "leak" into the bloodstream. Myoglobin, the muscle-cell equivalent of hemoglobin in the blood, is one of these components. Myoglobin is filtered from the blood by the kidneys and deposited in the urine, causing myoglobinuria. Dark-colored urine is the typical sign of myoglobinuria. Severe and/or repeated episodes of rhabdomyolysis and myoglobinuria can cause serious kidney damage.

Genetic profile

CPT-I deficiency is caused by defects in the CPT1 **gene** located on chromosome 11. CPT-II deficiency results from mutations in the CPT2 gene on chromosome 1.

Both CPT-I and CPT-II deficiency are considered autosomal recessive conditions. This means that both parents of an affected person carry one defective CPT gene, but also have a normal gene of that pair. Carriers of a single recessive gene typically do not express the deficiency because the second normal functioning gene, is able to compensate. A person with two mutated genes has no normal gene to make up for the deficiency, and thus expresses the disease. Parents who are both carriers for the same autosomal recessive condition face a 25% chance in each pregnancy that they will both pass on the defective gene and have an affected child.

Several individuals proven to be carriers of CPT-II deficiency have had mild symptoms of the disorder. Measurement of CPT-II enzyme levels (the protein coded for by CPT2) in most of the carriers tested show lower levels, as would be expected when one gene is mutated and the other is not. It is not yet clear why some carriers show mild symptoms, but this phenomenon occasionally occurs in other autosomal recessive conditions.

Demographics

CPT-I deficiency is rare, with fewer than 15 cases having been reported. CPT-II deficiency is more common, but its true occurrence is unknown. Muscle CPT-II deficiency makes up the majority of cases that have been reported; liver and multiorgan CPT-II deficiency are both quite rare. There seems to be no geographic area or ethnic group that is at greater risk for either type of CPT deficiency.

Approximately equal numbers of males and females with CPT-I deficiency have been seen, which is typical of autosomal recessive **inheritance**. However, about 80% of those individuals diagnosed with CPT-II deficiency are male. Males and females do have an equal likelihood of inheriting a defective CPT2 gene from a parent, but effects of the gene in each sex can be different. Hormonal differences between males and females may have some effect—a clue being the tendency of an affected woman to have more symptoms while pregnant.

Signs and symptoms

CPT-I deficiency

The CPT-I enzyme has two forms, coded for by different genes. CPT-IA is the form present in liver, skin, kidney, and heart cells, while CPT-IB functions in skeletal muscle, heart, fat, and testis cells. CPT-I deficiency refers to the CPT-IA form since a defective CPT-IB enzyme has not yet been described in humans. CPT-I deficiency has always been diagnosed in infants or children.

The brain and muscles use ketone bodies as a source of energy. The brain especially, relies heavily on ketone bodies for energy during times of stress, such as after fasting when low sugar levels (hypoglycemia) occur. In fact, children with CPT-I deficiency are usually first diagnosed after they have fasted due to an illness or diarrhea. Hypoketosis and hypoglycemia in CPT-I deficiency can become severe, and result in lethargy (lack of physical energy), seizures, and coma.

CPT-II deficiency

CPT-II deficiency is divided into three subtypes. "Muscle CPT deficiency" is the most common form of the condition. Onset of symptoms is usually in adolescence or adulthood, but varies. "Hepatic CPT-II deficiency" is rare and is diagnosed in childhood. The remaining cases are classified as "Multiorgan CPT-II deficiency," and have been diagnosed in infants. Differences in the severity of symptoms between the groups, as well as within each group, are due in part to different mutations in the CPT2 gene. Environmental factors may assist the triggering of attacks and thus may contribute to the variety of observed symptoms.

MUSCLE CPT DEFICIENCY Muscle fatigue, pain, and stiffness are typically caused by prolonged exercise or exertion. Other possible triggers include fasting, infection, muscle injury, exposure to cold, and even emotional stress. Cases of adverse reactions to certain types of general anesthesia have also been reported.

These muscle "attacks" after a triggering event are the classic physical signs of muscle CPT-II deficiency. When an attack is associated with the breakdown of muscle tissue (rhabdomyolysis), myoglobinuria is the other classic sign. Unlike other metabolic myopathies, there are no obvious signs of an impending attack, and resting will not stop the symptoms once they have begun. Muscle symptoms may begin during or up to several hours after prolonged exercise or other triggering events. A specific muscle group may be affected, or generalized symptoms may occur. Muscle weakness between attacks is not a problem, unlike some other metabolic myopathies. In addition, muscle cells examined under the microscope typically appear normal. Some people with muscle CPT deficiency have only had a few attacks in their lifetime, while others may experience several attacks per week. **Renal failure** due to repeated episodes of myoglobinuria occurs in about 25% of individuals with muscle CPT deficiency.

HEPATIC CPT-II DEFICIENCY Symptoms and age of onset in hepatic CPT-II deficiency are similar to CPT-I deficiency, primarily, coma and seizures associated with hypoketotic hypoglycemia. However, unlike CPT-I deficiency, most infants with liver CPT-II deficiency have had heart problems and have died.

MULTIORGAN CPT-II DEFICIENCY This type of CPT-II deficiency has only been reported a few times and involves the liver, skeletal muscles and heart. Infants with this type have all died.

KEY TERMS

Carnitine—An amino acid necessary for metabolism of the long-chain fatty acid portion of lipids. Also called vitamin B_7.

Fatty acids—The primary component of fats (lipids) in the body. Carnitine palmitoyl transferase (CPT) deficiency involves abnormal metabolism of the long-chain variety of fatty acids.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Hypoketosis—Decreased levels of ketone bodies.

Ketone bodies—Products of fatty acid metabolism in the liver that can be used by the brain and muscles as an energy source.

Metabolic myopathies—A broad group of muscle diseases whose cause is a metabolic disturbance of some type.

Mitochondria—Organelles within the cell responsible for energy production.

Myoglobinuria—The abnormal presence of myoglobin, a product of muscle disintegration, in the urine. Results in dark-colored urine.

Myopathy—Any abnormal condition or disease of the muscle.

Rhabdomyolysis—Breakdown or disintegration of muscle tissue.

Diagnosis

The symptoms of CPT-I deficiency can be dramatic, but the rare nature of the disease means that some time

may elapse while other more common diseases are ruled out. Definitive diagnosis of CPT-I deficiency is made by measuring the activity of the CPT enzyme in fibroblasts, leukocytes, or muscle tissue. Abnormal results on several blood tests are also typical of CPT-I deficiency, but the most important finding is hypoketotic hypoglycemia. Analysis of the CPT1 gene on chromosome 11 may be possible, but is not yet considered a diagnostic test.

CPT-II deficiency is somewhat more common than CPT-I deficiency. However, the milder symptoms of muscle CPT deficiency and their similarity to other diseases often leads to a wrong diagnosis (misdiagnosis). For example, the symptoms of CPT-II deficiency are sometimes initially diagnosed as fibromyalgia or chronic fatigue syndrome. Misdiagnosis is a special concern for people with muscle CPT-II deficiency, since the use of available preventive measures and treatment are then delayed.

Analysis of the CPT-II enzyme levels can confirm the diagnosis, but must be done carefully if performed on any tissue other than a muscle specimen. Direct testing of the CPT2 gene is available and is probably the easiest method (simple blood sample) of making the diagnosis. If **genetic testing** shows two mutated CPT2 genes, the diagnosis is confirmed. However, not all disease-causing mutations in the gene have been discovered, so demonstration of only one mutated CPT2 gene, or a completely negative test, does not exclude the diagnosis. In those individuals in whom genetic testing is not definitive, the combination of clinical symptoms and a laboratory finding of low levels of CPT-II enzyme activity should be enough to confirm the diagnosis.

Treatment and management

While CPT-I and CPT-II deficiency differ in their typical age of onset and in the severity of the symptoms, treatment of both conditions is similar. Attacks may be prevented by avoiding those situations that lead to them, as noted above. Someone undergoing surgery should discuss the possibility of alternative anesthetics with their doctor. Most people with CPT deficiency find it necessary to carry or wear some type of identifying information about their condition such as a Medic-Alert bracelet.

Those who find that they cannot avoid a situation known to be a trigger for them should try to supplement their diet with carbohydrates. Since medium-chain fatty acids to not require carnitine to enter the mitochondrion, use of a dietary supplement containing them results in significant improvement in people with CPT-I deficiency and also helps prevent attacks in most people with CPT-II deficiency. The use of carnitine supplements (vitamin B_7) is also helpful for some individuals diagnosed with the deficiency.

Anyone diagnosed with CPT deficiency, or anyone concerned about a family history of CPT deficiency, should be offered **genetic counseling** to discuss the most up-to-date treatment and testing options available to them.

Prognosis

Children with CPT-I deficiency improve significantly with treatment. So far, however, all have had some lasting neurological problems, possibly caused by damage to the brain during their first attack. The outlook at this point for infants and children with liver and multiorgan CPT-II deficiency is still poor.

Once a person with muscle CPT-II deficiency is correctly diagnosed, the prognosis is good. While it is impossible for many patients to completely avoid attacks, most people with the condition eventually find the right mix of preventive measures and treatments. CPT-II deficiency then has much less of a harmful impact on their lives. A number of excellent sources of information are available for families affected by CPT deficiency. Any new treatments in the future would likely attempt to directly address the enzyme deficiency, so that normal metabolism of lipids might occur.

Resources

ORGANIZATIONS

Fatty Oxidation Disorders (FOD) Family Support Group. Deb Lee Gould, MEd, Director, FOD Family Support Group, MCAD Parent and Grief Consultant, 805 Montrose Dr., Greensboro, NC 24710. (336) 547-8682. <http://www.fodsupport.org>.

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937 info@geneticalliance. <http://www.geneticalliance.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. <http://www.nsgc.org/GeneticCounselingYou.asp>.

United Mitochondrial Disease Foundation. PO Box 1151, Monroeville, PA 15146-1151. (412) 793-8077. Fax: (412) 793-6477. <http://www.umdf.org>.

OTHER

The Spiral Notebook—short takes on carnitine palmitoyl transferase deficiency. <http://www.spiralnotebook.org>

Scott J. Polzin, MS, CGC

Carpenter syndrome

Definition

Carpenter syndrome is a rare hereditary disorder resulting in the premature closing of the cranial sutures, which are the line joints between the bones of the skull, and in syndactyly, a condition characterized by the webbing of fingers and toes. The syndrome is named after G. Carpenter who first described this disorder in 1901.

Description

Carpenter syndrome is a subtype of a family of **genetic disorders** known as acrocephalopolysyndactyly (ACPS) disorders. Carpenter syndrome is also called Acrocephalopolysyndactyly Type II (ACPS II). There were originally five types of ACPS. As of early 2001, this number has decreased because some of these conditions have been recognized as being similar to each other or to other genetic syndromes. For example, it is now agreed that ACPS I, or Noack syndrome, is the same as **Pfeiffer syndrome**. Researchers have also concluded that the disorders formerly known as Goodman syndrome (ACPS IV) and Summitt syndrome are variants (slightly different forms) of Carpenter syndrome.

All forms of ACPS are characterized by premature closing of the cranial sutures and malformations of the fingers and toes. Individuals diagnosed with Carpenter syndrome have short and broad heads (brachycephaly), the tops of which appear abnormally cone-shaped (acrocephaly). Webbing or fusion of the fingers or toes (syndactyly) and/or the presence extra fingers or toes (polydactyly) are also characteristic signs of Carpenter syndrome.

The human skull consists of several bony plates separated by a narrow fibrous joint that contains stem cells. These fibrous joints are called cranial sutures. There are six sutures: the sagittal, which runs from front to back across the top of the head; the two coronal sutures, which run across the skull parallel to and just above the hairline; the metopic, which runs from front to back in front of the sagittal suture; and the two lamboid sutures, which run side to side across the back of the head. The premature closing of one or more of these cranial sutures leads to skull deformations, a condition called **craniosynostosis**. There are seven types of craniosynostosis depending on which cranial suture or sutures are affected: sagittal, bicoronal (both coronal sutures), unicoronal (one coronal suture), coronal and sagittal, metopic, lambdoid and sagittal, and total, in which all the cranial sutures are affected. Individuals affected with Carpenter syndrome show sagittal and bicoronal types of skull malformations.

Genetic profile

Carpenter syndrome is inherited as a recessive non-sex linked (autosomal) condition. The **gene** responsible for the syndrome has not yet been identified, but it is currently believed that all ACPS syndromes may be the result of genetic mutations—changes occurring in the genes. Genetic links to other syndromes that also result in craniosynostosis have been identified. As of 1997, 64 distinct mutations in six different genes have been linked to craniosynostosis. Three of these genes, one located on the short arm of chromosome 8 (8p11), one on the long arm of chromosome 10 (10q26), and another on the short arm of chromosome 4 (4p16), are related to fibroblast growth factor receptors (FGFRs), which are molecules that control cell growth. Other implicated genes are the TWIST gene located on chromosome 7, the MSX2 gene on chromosome 5, and the FBN1 gene on the long arm of chromosome 15.

Demographics

Carpenter syndrome and the other ACPS disorders have an occurrence of approximately one in every one million live births. It is rare because both parents must carry the **gene mutation** in order for their child to have the disease. Therefore, Carpenter syndrome has been observed in cases where the parents are related by blood, though in most cases parents are not related. Parents with one child affected by Carpenter syndrome have a 25% likelihood that their next child will also be affected with the disorder.

Signs and symptoms

Individuals diagnosed with Carpenter syndrome show various types of malformations and deformities of the skull. The two main examples are sagittal and bicoronal craniosynostosis. Sagittal craniosynostosis is characterized by a long and narrow skull (scaphocephaly). This is measured as an increase in the A-P, or anterior-to-posterior, diameter, which indicates that looking down on the top of the skull, the diameter of the head is greater than normal in the front-to-back orientation. Individuals affected with sagittal craniosynostosis also have narrow but prominent foreheads and a larger than normal back of the head. The so-called soft-spot found just beyond the hairline in a normal baby is very small or absent in a baby affected with sagittal craniosynostosis.

The other type of skull malformation observed, bicoronal craniosynostosis, is characterized by a wide

KEY TERMS

Acrocephalopolysyndactyly syndromes—A collection of genetic disorders characterized by cone-shaped abnormality of the skull and partial fusing of adjacent fingers or toes.

Acrocephaly—An abnormal cone shape of the head.

Autosome—Chromosome not involved in specifying sex.

Brachycephaly—An abnormal thickening and widening of the skull.

Cranial suture—Any one of the seven fibrous joints between the bones of the skull.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Cutaneous syndactyly—Fusion of the soft tissue between fingers or toes resulting in a webbed appearance.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Polydactyly—The presence of extra fingers or toes.

Scaphocephaly—An abnormally long and narrow skull.

Syndactyly—Webbing or fusion between the fingers or toes.

and short skull (brachycephaly). This is measured as a decrease in the A-P diameter, which indicates that looking down on the top of the skull, the diameter of the head is less than normal in the front-to-back orientation. Individuals affected with this condition have poorly formed eye sockets and foreheads. This causes a smaller than normal sized eye socket that can cause eyesight complications. These complications include damage to the optic nerve, which can cause a loss of visual clarity; bulging eyeballs resulting from the shallow orbits (exophthalmus), which usually damages the eye cornea; widely spaced eyes; and a narrowing of the sinuses and tear ducts that can cause inflammation of the mucous membranes that line the exposed portion of the eyeball (conjunctivitis).

A further complication of bicoronal craniosynostosis is water on the brain (**hydrocephalus**), which increases pressure on the brain. Most individuals affected with this condition also have an abnormally high and arched palate that can cause dental problems and protrusion, the thrusting forward of the lower jaw. Coronal and sagittal craniosynostosis are characterized by a cone-shaped head (acrocephaly). The front soft-spot characteristic of an infant's skull is generally much larger than normal and it may never close without surgical intervention. Individuals with these skull abnormalities may also have higher than normal pressure inside the skull.

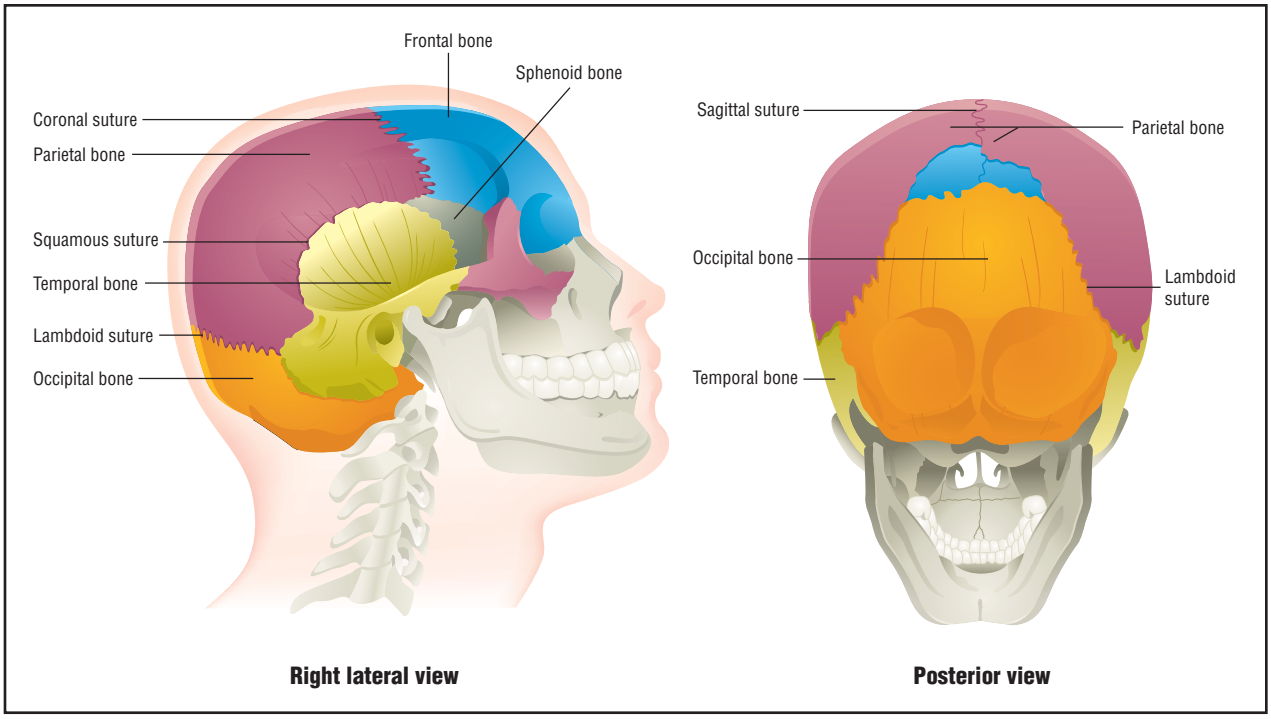
Individuals with Carpenter syndrome often have webbed fingers or toes (cutaneous syndactyly) or partial fusion of their fingers or toes (syndactyly). These individuals also tend to have unusually short fingers (bracydactyly) and sometimes exhibit extra toes, or more rarely, extra fingers (polydactyly).

Approximately one third of Carpenter syndrome individuals have heart defects at birth. These may include: narrowing of the artery that delivers blood from the heart to the lungs (pulmonary stenosis); blue baby syndrome, due to various defects in the structure of the heart or its major blood vessels; transposition of the major blood vessels, meaning that the aorta and pulmonary artery are inverted; and the presence of an extra large vein, called the superior vena cava, that delivers blood back to the heart from the head, neck, and upper limbs.

In some persons diagnosed with Carpenter syndrome, additional physical problems are present. Individuals are often short or overweight, with males having a disorder in which the testicles fail to descend properly (cryptorchidism). Another problem is caused by parts of the large intestine coming through an abnormal opening near the navel (umbilical hernia). In some cases, mild mental retardation has also been observed.

Diagnosis

The diagnosis of Carpenter syndrome is made based on the presence of the bicoronal and sagittal skull malformation, which produces a cone-shaped or short and broad skull, accompanied by partially fused or extra fingers or toes (syndactly or polydactyly). Skull x rays and/or a CT scan may also be used to diagnose the skull malformations correctly. Other genetic disorders are also characterized by the same types of skull deformities and some genetic tests are available for them. Thus, positive results on these tests can rule out the possibility of Carpenter syndrome.



Right lateral and posterior view of the skull with sutures identified. *(Gale Group)*

Before birth, ultrasound imaging, a technique used to produce pictures of the fetus, is generally used to examine the development of the skull in the second and third months of pregnancy, but the images are not, as of 2000, always clear enough to properly diagnose the type of skull deformity, if present. New ultrasound techniques are being used in Japan however, that can detect skull abnormalities in fetuses with much higher image clarity.

Treatment and management

Operations to correct the skull malformations associated with Carpenter syndrome should be performed during the first year of the baby's life. This is because modifying the skull bones is much easier at that age and new bone growth, as well as the required bone reshaping, can occur rapidly. Also, the facial features are still highly undeveloped, so a greatly improved appearance can be achieved. If heart defects are present at birth, surgery may also be required. Follow-up support by pediatric, psychological, neurological, surgical, and genetic specialists may be necessary.

Individuals with Carpenter syndrome may have vision problems that require consultation with an ophthalmologist, or doctor specialized in the treatment of such problems. Speech and hearing therapy may also be necessary if the ears and the brain have been affected. If the palate is severely malformed, dental consultation may also be necessary. In the most severe cases of Carpenter syndrome, it may be necessary to treat feeding and respiratory problems that are associated with the malformed palate and sinuses. Obesity is associated with Carpenter syndrome and dietary management throughout the patient's lifetime may also be recommended.

Webbed fingers or toes (cutaneous syndactyly) may be easily corrected by surgery. Extra fingers or toes (polydactyly) may often be surgically removed shortly after birth.

Surgical procedures also exist to correct some of the heart defects associated with Carpenter syndrome, as well as the testicles disorder of affected males. The abnormal opening of the large intestine near the navel (umbilical hernia or **omphalocele**) can also be treated by surgery. Additionally, intervention programs for developmental delays are available for affected patients.

Prognosis

Carpenter syndrome is not usually fatal if immediate treatment for the heart defects and/or skull malformations is available. In all but the most severe and inoperable cases of craniosynostosis, it is possible that the affected individual may attain a greatly improved physical appearance. Depending on damage to the nervous system, the rapidity of treatment, and the potential brain damage from excess pressure on the brain caused by skull mal-

formation, certain affected individuals may display varying degrees of developmental delay. Some individuals will continue to have vision problems throughout life. These problems will vary in severity depending on the initial extent of their individual skull malformations, but most of these problems can now be treated.

Resources

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ORGANIZATIONS

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

Craniosynostosis and Parents Support. 2965-A Quarters, Quantico, VA 22134. (877) 686-CAPS or (703) 445-1078. <http://www.caps2000.org/>.

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Paul A. Johnson

Cat cry syndrome *see* **Cri du chat syndrome**

Celiac disease

Definition

Celiac disease is a disease of the digestive system that damages the small intestine and interferes with the absorption of nutrients from food.

Description

Celiac disease occurs when the body reacts abnormally to gluten, a protein found in wheat, rye, barley, and possibly oats. When someone with celiac disease eats foods containing gluten, that person's immune system causes an inflammatory response in the small intestine, which damages the tissues and results in an impaired ability to absorb nutrients from foods. The inflammation and malabsorption create wide-ranging problems in many systems of the body. Since the body's own immune system causes the damage, celiac disease is classified as an "autoimmune" disorder. Celiac disease may also be called sprue, nontropical sprue, gluten sensitive enteropathy, celiac sprue, and adult celiac disease.

Genetic profile

Celiac disease can run in families and has a genetic basis, but the pattern of **inheritance** is complicated. The type of inheritance pattern that celiac disease follows is called multifactorial (caused by many factors, both genetic and environmental). Researchers think that several factors must exist in order for the disease to occur. First, the patient must have a genetic predisposition to develop the disorder. Then, something in their environment acts as a stimulus to "trigger" their immune system, causing the disease to become active for the first time. For conditions with **multifactorial inheritance**, people without the genetic predisposition are less likely to develop the condition with exposure to the same triggers. Or, they may require more exposure to the stimulus before developing the disease than someone with a genetic predisposition. Several factors may provoke a reaction including surgery, especially gastrointestinal surgery; a change to a low fat diet, which has an increased number of wheat-based foods; pregnancy; childbirth; severe emotional stress; or a viral infection. This combination of genetic susceptibility and an outside agent leads to celiac disease.

Demographics

Celiac disease may be discovered at any age, from infancy through adulthood. The disorder is more commonly found among white Europeans or in people of European descent. It is very unusual to find celiac disease in African or Asian people. The exact incidence of the disease is uncertain. Estimates vary from one in 5,000, to as many as one in every 300 individuals with this background. The prevalence of celiac disease seems to be different from one European country to another, and between Europe and the United States. This may be due to differences in diet and/or unrecognized disease. A recent study of random blood samples tested for celiac disease in the United States showed one in 250 testing positive. It is clearly underdiagnosed, probably due to the symptoms being attributed to another problem, or lack of

knowledge about celiac disease by physicians and laboratories.

Because celiac disease has a hereditary influence, close relatives (especially first degree relatives, such as children, siblings, and parents) have a higher risk of being affected with the condition. The chance that a first degree relative of someone with celiac disease will have the disease is about 10%.

As more is learned about celiac disease, it becomes evident that there are many variations which may not produce typical symptoms. It may even be clinically "silent," where no obvious problems related to the disease are apparent.

KEY TERMS

Antibodies—Proteins that provoke the immune system to attack particular substances. In celiac disease, the immune system makes antibodies to a component of gluten.

Gluten—A protein found in wheat, rye, barley, and oats.

Villi—Tiny, finger-like projections that enable the small intestine to absorb nutrients from food.

Signs and symptoms

Each person with celiac disease is affected differently. When food containing gluten reaches the small intestine, the immune system begins to attack a substance called gliadin, which is found in the gluten. The resulting inflammation causes damage to the delicate finger-like structures in the intestine, called villi, where food absorption actually takes place. The patient may experience a number of symptoms related to the inflammation and the chemicals it releases, and or the lack of ability to absorb nutrients from food, which can cause malnutrition.

The most commonly recognized symptoms of celiac disease relate to the improper absorption of food in the gastrointestinal system. Many patients with gastrointestinal symptoms will have diarrhea and fatty, greasy, unusually foul-smelling stools. The patient may complain of excessive gas (flatulence), distended abdomen, weight loss, and generalized weakness. Not all people have digestive system complications; some people only have irritability or **depression**. Irritability is one of the most common symptoms in children with celiac disease.

Not all patients have these problems. Unrecognized and untreated celiac disease may cause or contribute to a variety of other conditions. The decreased ability to digest, absorb, and utilize food properly (malabsorption) may cause anemia (low red blood count) from iron deficiency or easy bruising from a lack of vitamin K. Poor mineral absorption may result in osteoporosis, or "brittle bones," which may lead to bone fractures. Vitamin D levels may be insufficient and bring about a "softening" of bones (osteomalacia), which produces pain and bony deformities, such as flattening or bending. Defects in the tooth enamel, characteristic of celiac disease, may be recognized by dentists. Celiac disease may be discovered during medical tests performed to investigate failure to thrive in infants, or lack of proper growth in children and adolescents. People with celiac disease may also experience lactose intolerance because they do not produce enough of the enzyme lactase, which breaks down the sugar in milk into a form the body can absorb. Other symptoms can include, muscle cramps, fatigue, delayed growth, tingling or numbness in the legs (from nerve damage), pale sores in the mouth (called aphthus ulcers), tooth discoloration, or missed menstrual periods (due to severe weight loss).

A distinctive, painful skin rash, called dermatitis herpetiformis, may be the first sign of celiac disease. Approximately 10% of patients with celiac disease have this rash, but it is estimated that 85% or more of patients with the rash have the disease.

Many disorders are associated with celiac disease, though the nature of the connection is unclear. One type of **epilepsy** is linked to celiac disease. Once their celiac disease is successfully treated, a significant number of these patients have fewer or no seizures. Patients with alopecia areata, a condition where hair loss occurs in sharply defined areas, have been shown to have a higher risk of celiac disease than the general population. There appears to be a higher percentage of celiac disease among people with **Down syndrome**, but the link between the conditions is unknown.

Several conditions attributed to a disorder of the immune system have been associated with celiac disease. People with insulin dependent diabetes (type I) have a much higher incidence of celiac disease. One source estimates that as many as one in 20 insulin-dependent diabetics may have celiac disease. Patients with juvenile chronic arthritis, some thyroid diseases, and IgA deficiency are also more likely to develop celiac disease.

There is an increased risk of intestinal lymphoma, a type of **cancer**, in individuals with celiac disease. Successful treatment of the celiac disease seems to decrease the chance of developing lymphoma.

Diagnosis

Because of the variety of ways celiac disease can manifest itself, it is often not discovered promptly. Its symptoms are similar to many other conditions including irritable bowel syndrome, Crohn's disease, ulcerative colitis, diverticulosis, intestinal infections, chronic fatigue syndrome, and depression. The condition may persist without diagnosis for so long that the patient accepts a general feeling of illness as normal. This leads to further delay in identifying and treating the disorder. It is not unusual for the disease to be identified in the course of medical investigations for seemingly unrelated problems. For example, celiac disease has been discovered during testing to find the cause of infertility.

If celiac disease is suspected, a blood test can be ordered. This test looks for the antibodies to gluten (called antigliadin, anti-endomysium, and antireticulin) that the immune system produces in celiac disease. Antibodies are chemicals produced by the immune system in response to substances that the body perceives to be threatening. Some experts advocate not just evaluating patients with symptoms, but using these blood studies as a screening test for high-risk individuals, such as those with relatives (especially first degree relatives) known to have the disorder. An abnormal result points towards celiac disease, but further tests are needed to confirm the diagnosis. Because celiac disease affects the ability of the body to absorb nutrients from food, several tests may be ordered to look for nutritional deficiencies. For example, doctors may order a test of iron levels in the blood because low levels of iron (anemia) may accompany celiac disease. Doctors may also order a test for fat in the stool, since celiac disease prevents the body from absorbing fat from food.

If these tests are suspicious for celiac disease, the next step is a biopsy (removal of a tiny piece of tissue surgically) of the small intestine. This is usually done by a gastroenterologist, a physician who specializes in diagnosing and treating bowel disorders. It is generally performed in the office, or in a hospital's outpatient department. The patient remains awake, but is sedated. A narrow tube, called an endoscope, is passed through the mouth, down through the stomach, and into the small intestine. A small sample of tissue is taken and sent to the laboratory for analysis. If it shows a pattern of tissue damage characteristic of celiac disease, the diagnosis is established.

The patient is then placed on a gluten-free diet (GFD). The physician will periodically recheck the level of antibodies in the patient's blood. After several months, the small intestine is biopsied again. If the diagnosis of celiac disease was correct (and the patient followed the rigorous diet), healing of the intestine will be apparent. Most experts agree that it is necessary to follow these steps in order to be sure of an accurate diagnosis.

Treatment and management

The only treatment for celiac disease is a gluten-free diet. This may be easy for the doctor to prescribe, but difficult for the patient to follow. For most people, adhering to this diet will stop symptoms and prevent damage to the intestines. Damaged villi can be functional again in three to six months. This diet must be followed for life. For people whose symptoms are cured by the gluten-free diet, this is further evidence that their diagnosis is correct.

Gluten is present in any product that contains wheat, rye, barley, or oats. It helps make bread rise, and gives many foods a smooth, pleasing texture. In addition to the many obvious places gluten can be found in a normal diet, such as breads, cereals, and pasta, there are many hidden sources of gluten. These include ingredients added to foods to improve texture or enhance flavor and products used in food packaging. Gluten may even be present on surfaces used for food preparation or cooking.

Fresh foods that have not been artificially processed, such as fruits, vegetables, and meats, are permitted as part of a GFD. Gluten-free foods can be found in health food stores and in some supermarkets. Mail-order food companies often have a selection of gluten-free products. Help in dietary planning is available from dieticians (health care professionals specializing in food and nutrition) or from support groups for individuals with celiac disease. There are many cookbooks on the market specifically for those on a GFD.

Treating celiac disease with a GFD is almost always completely effective. Gastrointestinal complaints and other symptoms are alleviated. Secondary complications, such as anemia and osteoporosis, resolve in almost all patients. People who have experienced lactose intolerance related to their celiac disease usually see those symptoms subside as well. Although there is no risk and much potential benefit to this treatment, it is clear that avoiding all foods containing gluten can be difficult.

Experts emphasize the need for lifelong adherence to the GFD to avoid the long-term complications of this disorder. They point out that although the disease may have symptom-free periods if the diet is not followed, silent damage continues to occur. Celiac disease cannot be "outgrown" or cured, according to medical authorities.

Prognosis

Patients with celiac disease must adhere to a strict GFD throughout their lifetime. Once the diet has been

followed for several years, individuals with celiac disease have similar mortality rates as the general population. However, about 10% of people with celiac disease develop a cancer involving the gastrointestinal tract (both carcinoma and lymphoma).

There are a small number of patients who develop a refractory type of celiac disease, where the GFD no longer seems effective. Once the diet has been thoroughly assessed to ensure no hidden sources of gluten are causing the problem, medications may be prescribed. Steroids or immunosuppressant drugs are often used to try to control the disease. It is unclear whether these efforts meet with much success.

Prevention

There is no way to prevent celiac disease. However, the key to decreasing its impact on overall health is early diagnosis and strict adherence to the prescribed gluten-free diet.

Resources

BOOKS

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Pruessner, H. "Detecting Celiac Disease in Your Patients." *American Family Physician* 57 (March 1998): 1023–34.

ORGANIZATIONS

American Celiac Society. 58 Musano Court, West Orange, NJ, 7052. (201) 325-8837.

Celiac Disease Foundation. 13251 Ventura Blvd., Suite 1, Studio City, CA 91604-1838. (818) 990-2354. <http://www.cdf@celiac.org>.

Celiac Sprue Association/United State of America (CSA/USA). PO Box 31700, Omaha, NE 68131-0700. (402) 558-0600.

Gluten Intolerance Group. PO Box 23053, Seattle, WA, 98102-0353. (206) 325-6980.

National Center for Nutrition and Dietetics. American Dietetic Association, 216 West Jackson Boulevard, Suite 800, Chicago, IL, 60606-6995. (800) 366-1655.

WEBSITES

National Institute of Diabetes & Digestive & Kidney Diseases. <http://www.niddk.nih.gov/health/digest/pubs/celiac/index.htm>.

Amy Vance, MS, CGC

Central core disease

Definition

Central core disease (CCD) is an inherited muscle disorder that affects many of the voluntary muscles necessary for movement. The hips and legs are particularly affected. Although central core disease is disabling, it is not fatal.

Description

First described in 1956, central core disease is one of a group of muscle disorders, or myopathies, named for certain abnormalities found in the muscle biopsies of people with the syndrome. CCD occurs when the central parts, or cores, of certain muscle cells are metabolically inactive, meaning they do not produce energy correctly. This happens because the cores lack a substance called mitochondria, the energy-producing parts of the muscle cells.

According to the Muscular Dystrophy Association, a muscle cell produces thousands of proteins during its lifetime. With all of the inheritable diseases of muscle, an altered **gene** leads to an absence of, or abnormality in, one of the proteins necessary for normal functioning of a muscle cell.

Scientists are pursuing a number of promising leads in their quest to understand the causes of CCD. New research suggests that muscle cells that have difficulty regulating calcium may cause central core disease.

Although CCD is not a progressive illness, different people experience varying degrees of weakness. Some children with CCD show mildly delayed motor milestones, then catch up and appear only slightly uncoordinated. Others have more severe delays, but also catch up somewhat and are able to walk and move about, although with more limitations. Some children use braces for walking, and a few use wheelchairs.

Genetic profile

Central core disease is inherited as a dominant trait, meaning that an individual with CCD has a 50% chance of passing the disorder on to each child. There are also occurrences of sporadic **inheritance**, which means that a gene alters spontaneously to cause the disorder in a person with no family history of the disease. In 1993, researchers identified the abnormal gene responsible for CCD. This finding has been important in understanding what causes central cores in the muscle and why the muscles of people with CCD are weak. According to scientific findings, an abnormality in a gene on chromosome 19 may lead to the disease.

KEY TERMS

Dominant trait—A genetic trait where one copy of the gene is sufficient to yield an outward display of the trait; dominant genes mask the presence of recessive genes; dominant traits can be inherited from a single parent.

Malignant hyperthermia—A condition brought on by anesthesia during surgery.

Mitochondria—Organelles within the cell responsible for energy production.

Myopathy—Any abnormal condition or disease of the muscle.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Sporadic inheritance—A status that occurs when a gene mutates spontaneously to cause the disorder in a person with no family history of the disorder.

Demographics

The disease becomes noticeable in early childhood, when muscle cramps are often present after exercising or performing other physical activities. Central core disease is often seen as "floppiness" in a newborn baby, followed by periods of persistent muscle weakness.

Signs and symptoms

Symptoms of central core disease are usually not severe; however, the disease can be disabling. A mild general weakness and hip displacement are key characteristics of the disease. Individuals with CCD reach motor skill milestones much later than those without the disorder. A child with the disease cannot run easily, and jumping and other physical activities are often impossible.

Other long-term problems caused by CCD include hip dislocation and curvature of the spine, a condition known as **scoliosis**. Central core disease also causes skin rash, muscular shrinkage, endocrine abnormalities, heart problems, or mental problems.

Diagnosis

The diagnosis of central core disease is made after several neurological tests are completed. These tests involve checking an individual's coordination, tendon reflexes such as the knee-jerk reaction, walking ability, and the ability to rise from a sitting position. A serum enzyme test might also be performed to measure how much muscle protein is circulating through the blood.

Treatment and management

Treatment measures greatly depend on the severity of the individual's symptoms, especially the degree of muscle weakness that is involved. Treatment measures include surgical procedures, pain management, muscle stimulation therapy, and physical therapy.

According to the Muscular Dystrophy Association, people who have central core disease are sometimes vulnerable to **malignant hyperthermia** (MH), a condition brought on by anesthesia during surgery. Malignant hyperthermia causes a rapid, and sometimes fatal, rise in body temperature, producing muscle stiffness. When susceptible individuals are exposed to the most commonly used general anesthetic, their muscles can become rigid and their body temperatures can rise to dangerous levels.

Prognosis

Fortunately, the outlook for children with this disease is generally positive. Although children with central core disease start their life with some developmental delays, many improve as they get older and stay active throughout their lives.

Resources

ORGANIZATIONS

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

WEBSITES

Coping with Central Core Disease. <http://www.mdausa.org/publications/Quest/q62ccd.html>.

Central Core Disease. <http://www.mdausa.org/disease/ccd.html>.

Bethanne Black

Central core disease of muscle *see* **Central core disease**

Cerebral giantism *see* **Sotos syndrome**

Cerebral palsy

Definition

Cerebral palsy (CP) is the term used for a group of nonprogressive disorders of movement and posture caused by abnormal development of, or damage to, motor control centers of the brain. CP is caused by events before, during, or after birth. The abnormalities of mus-

cle control that define CP are often accompanied by other neurological and physical abnormalities.

Description

Voluntary movement (walking, grasping, chewing, etc.) is primarily accomplished using muscles that are attached to bones, known as the skeletal muscles. Control of the skeletal muscles originates in the cerebral cortex, the largest portion of the brain. Palsy means paralysis, but may also be used to describe uncontrolled muscle movement. Therefore, cerebral palsy encompasses any disorder of abnormal movement and paralysis caused by abnormal function of the cerebral cortex. In truth, however, CP does not include conditions due to progressive disease or degeneration of the brain. For this reason, CP is also referred to as static (nonprogressive) encephalopathy (disease of the brain). Also excluded from CP are any disorders of muscle control that arise in the muscles themselves and/or in the peripheral nervous system (nerves outside the brain and spinal cord).

CP is not a specific diagnosis, but is more accurately considered a description of a broad but defined group of neurological and physical problems.

The symptoms of CP and their severity are quite variable. Those with CP may have only minor difficulty with fine motor skills, such as grasping and manipulating items with their hands. A severe form of CP could involve significant muscle problems in all four limbs, mental retardation, seizures, and difficulties with vision, speech, and hearing.

Muscles that receive abnormal messages from the brain may be constantly contracted and tight (spastic), exhibit involuntary writhing movements (athetosis), or have difficulty with voluntary movement (dyskinesia). There can also be a lack of balance and coordination with unsteady movements (ataxia). A combination of any of these problems may also occur. Spastic CP and mixed CP constitute the majority of cases. Effects on the muscles can range from mild weakness or partial paralysis (*paresis*), to complete loss of voluntary control of a muscle or group of muscles (*plegia*). CP is also designated by the number of limbs affected. For instance, affected muscles in one limb is monoplegia, both arms or both legs is diplegia, both limbs on one side of the body is hemiplegia, and in all four limbs is quadriplegia. Muscles of the trunk, neck, and head may be affected as well.

CP can be caused by a number of different mechanisms at various times—from several weeks after conception, through birth, to early childhood. For many years, it was accepted that most cases of CP were due to brain injuries received during a traumatic birth, known as birth asphyxia. However, extensive research in the 1980s showed that only 5–10% of CP can be attributed to birth trauma. Other possible causes include abnormal development of the brain, prenatal factors that directly or indirectly damage neurons in the developing brain, premature birth, and brain injuries that occur in the first few years of life.

Genetic profile

As noted, CP has many causes, making a discussion of the genetics of CP complicated. A number of hereditary/genetic syndromes have signs and symptoms similar to CP, but usually also have problems not typical of CP. Put another way, some hereditary conditions "mimic" CP. Isolated CP, meaning CP that is not a part of some other syndrome or disorder, is usually not inherited.

It might be possible to group the causes of CP into those that are genetic and those that are non-genetic, but most would fall somewhere in between. Grouping causes into those that occur during pregnancy (prenatal), those that happen around the time of birth (perinatal), and those that occur after birth (postnatal), is preferable. CP related to premature birth and multiple birth pregnancies (twins, triplets, etc.) is somewhat different and considered separately.

Prenatal causes

Although much has been learned about human embryology in the last couple of decades, a great deal remains unknown. Studying prenatal human development is difficult because the embryo and fetus develop in a closed environment—the mother's womb. However, the relatively recent development of a number of prenatal tests has opened a window on the process. Add to that more accurate and complete evaluations of newborns, especially those with problems, and a clearer picture of what can go wrong before birth is possible.

The complicated process of brain development before birth is susceptible to many chance errors that can result in abnormalities of varying degrees. Some of these errors will result in structural anomalies of the brain, while others may cause undetectable, but significant, abnormalities in how the cerebral cortex is "wired." An abnormality in structure or wiring is sometimes hereditary, but is most often due to chance, or a cause unknown at this time. Whether and how much genetics played a role in a particular brain abnormality depends to some degree on the type of anomaly and the form of CP it causes.

Several maternal-fetal infections are known to increase the risk for CP, including rubella (German measles, now rare in the United States), cytomegalovirus (CMV), and toxoplasmosis. Each of these infections is considered a risk to the fetus only if the mother contracts it for the first time during that pregnancy. Even in those

cases, though, most babies will be born normal. Most women are immune to all three infections by the time they reach childbearing age, but a woman's immune status can be determined using the TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes) test before or during pregnancy.

Just as a stroke can cause neurologic damage in an adult, so too can this type of event occur in the fetus. A burst blood vessel in the brain followed by uncontrolled bleeding (coagulopathy), known as intracerebral hemorrhage, could cause a fetal stroke, or a cerebral blood vessel could be obstructed by a clot (embolism). Infants who later develop CP, along with their mothers, are more likely than other mother-infant pairs to test positive for factors that put them at increased risk for bleeding episodes or blood clots. Some coagulation disorders are strictly hereditary, but most have a more complicated basis.

A **teratogen** is any substance to which a woman is exposed that has the potential to harm the embryo or fetus. Links between a drug or other chemical exposure during pregnancy and a risk for CP are difficult to prove. However, any substance that might affect fetal brain development, directly or indirectly, could increase the risk for CP. Furthermore, any substance that increases the risk for premature delivery and low birth weight, such as alcohol, tobacco, or cocaine, among others, might indirectly increase the risk for CP.

The fetus receives all nutrients and oxygen from blood that circulates through the placenta. Therefore, anything that interferes with normal placental function might adversely affect development of the fetus, including the brain, or might increase the risk for premature delivery. Structural abnormalities of the placenta, premature detachment of the placenta from the uterine wall (abruption), and placental infections (chorioamnionitis) are thought to pose some risk for CP.

Certain conditions in the mother during pregnancy might pose a risk to fetal development leading to CP. Women with autoimmune anti-thyroid or anti-phospholipid (APA) antibodies are at slightly increased risk for CP in their children. A potentially important clue uncovered recently points toward high levels of cytokines in the maternal and fetal circulation as a possible risk for CP. Cytokines are proteins associated with inflammation, such as from infection or autoimmune disorders, and they may be toxic to neurons in the fetal brain. More research is needed to determine the exact relationship, if any, between high levels of cytokines in pregnancy and CP. A woman has some risk of developing the same complications in more than one pregnancy, slightly increasing the risk for more than one child with CP.

Serious physical trauma to the mother during pregnancy could result in direct trauma to the fetus as well, or injuries to the mother could compromise the availability of nutrients and oxygen to the developing fetal brain.

Perinatal causes

Birth asphyxia significant enough to result in CP is now uncommon in developed countries. Tight nuchal cord (umbilical cord around the baby's neck) and prolapsed cord (cord delivered before the baby) are possible causes of birth asphyxia, as are bleeding and other complications associated with placental abruption and placenta previa (placenta lying over the cervix).

Infection in the mother is sometimes not passed to the fetus through the placenta, but is transmitted to the baby during delivery. Any such infection that results in serious illness in the newborn has the potential to produce some neurological damage.

Postnatal causes

The remaining 15% of CP is due to neurologic injury sustained after birth. CP that has a postnatal cause is sometimes referred to as acquired CP, but this is only accurate for those cases caused by infection or trauma.

Incompatibility between the Rh blood types of mother and child (mother Rh negative, baby Rh positive) can result in severe anemia in the baby (erythroblastosis fetalis). This may lead to other complications, including severe jaundice, which can cause CP. Rh disease in the newborn is now rare in developed countries due to routine screening of maternal blood type and treatment of pregnancies at risk. The routine, effective treatment of jaundice due to other causes has also made it an infrequent cause of CP in developed countries. Rh blood type poses a risk for recurrence of Rh disease if treatment is not provided.

Serious infections that affect the brain directly, such as meningitis and encephalitis, may cause irreversible damage to the brain, leading to CP. A seizure disorder early in life may cause CP, or may be the product of a hidden problem that causes CP in addition to seizures. Unexplained (idiopathic) seizures are hereditary in only a small percentage of cases. Although rare in infants born healthy at or near term, intracerebral hemorrhage and brain embolism, like fetal stroke, are sometimes genetic.

Physical trauma to an infant or child resulting in brain injury, such as from abuse, accidents, or near drowning/suffocation, might cause CP. Likewise, ingestion of a toxic substance such as lead, mercury, poisons, or certain chemicals could cause neurological damage. Accidental overdose of certain medications might also cause similar damage to the central nervous system.

Prematurity and multiple birth pregnancy

Advances in the medical care of premature infants in the last 20 years have dramatically increased the rate of

survival of these fragile newborns. However, as gestational age at delivery and birth weight of a baby decrease, the risk for CP dramatically increases. A term pregnancy is delivered at 37–41 weeks gestation. The risk for CP in a preterm infant (32–37 weeks) is increased about five-fold over the risk for an infant born at term. Survivors of extremely preterm births (less than 28 weeks) face as much as a fifty-fold increase in risk. About 50% of all cases of CP now being diagnosed are in children who were born prematurely.

Two factors are involved in the risk for CP associated with prematurity. First, premature babies are at higher risk for various CP-associated medical complications, such as intracerebral hemorrhage, infection, and difficulty in breathing, to name a few. Second, the onset of premature labor may be induced, in part, by complications that have already caused neurologic damage in the fetus. A combination of both factors almost certainly plays a role in some cases of CP. The tendency toward premature delivery tends to run in families, but the genetic mechanisms are far from clear.

An increase in multiple birth pregnancies in recent years, especially in the United States, is blamed on the increased use of fertility drugs. As the number of fetuses in a pregnancy increases, the risks for abnormal development and premature delivery also increase. Children from twin pregnancies have four times the risk of developing CP as children from singleton pregnancies, owing to the fact that more twin pregnancies are delivered prematurely. The risk for CP in a child of triplets is up to 18 times greater. Furthermore, recent evidence suggests that a baby from a pregnancy in which its twin died before birth is at increased risk for CP.

Demographics

Approximately 500,000 children and adults in the United States have CP, and it is newly diagnosed in about 6,000 infants and young children each year. The incidence of CP has not changed much in the last 20–30 years. Ironically, advances in medicine have decreased the incidence from some causes, Rh disease for example, but increased it from others, notably, prematurity and multiple birth pregnancies. No particular ethnic groups seem to be at higher risk for CP. However, people of disadvantaged background are at higher risk due to poorer access to proper prenatal care and advanced medical services.

Signs and symptoms

By definition, the defect in cerebral function causing CP is nonprogressive. However, the symptoms of CP often change over time. Most of the symptoms of CP relate in some way to the aberrant control of muscles. To review, CP is categorized first by the type of movement/postural disturbance(s) present, then by a description of which limbs are affected, and finally by the severity of motor impairment. For example, spastic diplegia refers to continuously tight muscles that have no vol-

KEY TERMS

Asphyxia—Lack of oxygen. In the case of cerebral palsy, lack of oxygen to the brain.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Athetosis—A condition marked by slow, writhing, involuntary muscle movements.

Cerebral palsy—Movement disability resulting from nonprogressive brain damage.

Coagulopathy—A disorder in which blood is either too slow or too quick to coagulate (clot).

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Cytokine—A protein associated with inflammation that, at high levels, may be toxic to nerve cells in the developing brain.

Diplegia—Paralysis affecting like parts on both sides of the body, such as both arms or both legs.

Dorsal rhizotomy—A surgical procedure that cuts nerve roots to reduce spasticity in affected muscles.

Dyskinesia—Impaired ability to make voluntary movements.

Hemiplegia—Paralysis of one side of the body.

Hypotonia—Reduced or diminished muscle tone.

Quadriplegia—Paralysis of all four limbs.

Serial casting—A series of casts designed to gradually move a limb into a more functional position.

Spastic—A condition in which the muscles are rigid, posture may be abnormal, and fine motor control is impaired.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Static encephalopathy—A disease of the brain that does not get better or worse.

Tenotomy—A surgical procedure that cuts the tendon of a contracted muscle to allow lengthening.

untary control in both legs, while athetoid quadraparesis describes uncontrolled writhing movements and muscle weakness in all four limbs. These three-part descriptions are helpful in providing a general picture, but cannot give a complete description of any one person with CP. In addition, the various "forms" of CP do not occur with equal frequency—spastic diplegia is seen in more individuals than is athetoid quadraparesis. CP can also be loosely categorized as mild, moderate, or severe, but these are very subjective terms with no firm boundaries between them.

A muscle that is tensed and contracted is hypertonic, while excessively loose muscles are hypotonic. Spastic, hypertonic muscles can cause serious orthopedic problems, including **scoliosis** (spine curvature), hip dislocation, or contractures. A contracture is shortening of a muscle, aided sometimes by a weak-opposing force from a neighboring muscle. Contractures may become permanent, or "fixed," without some sort of intervention. Fixed contractures may cause postural abnormalities in the affected limbs. Clenched fists and contracted feet (equinus or equinovarus) are common in people with CP. Spasticity in the thighs causes them to turn in and cross at the knees, resulting in an unusual method of walking known as a "scissors gait." Any of the joints in the limbs may be stiff (immobilized) due to spasticity of the attached muscles.

Athetosis and dyskinesia often occur with spasticity, but do not often occur alone. The same is true of ataxia. It is important to remember that "mild CP" or "severe CP" refers not only to the number of symptoms present, but also to the level of involvement of any particular class of symptoms.

Mechanisms that can cause CP are not always restricted to motor-control areas of the brain. Other neurologically–based symptoms may include:

- mental retardation/learning disabilities
- behavioral disorders
- seizure disorders
- visual impairment
- hearing loss
- speech impairment (dysarthria)
- abnormal sensation and perception

These problems may have a greater impact on a child's life than the physical impairments of CP, although not all children with CP are affected by other problems. Many infants and children with CP have growth impairment. About one-third of individuals with CP have moderate-to-severe mental retardation, one-third have mild mental retardation, and one-third have normal intelligence.

Diagnosis

The signs of CP are not usually noticeable at birth. Children normally progress through a predictable set of developmental milestones through the first 18 months of life. Children with CP, however, tend to develop these skills more slowly because of their motor impairments, and delays in reaching milestones are usually the first symptoms of CP. Babies with more severe cases of CP are normally diagnosed earlier than others.

Selected developmental milestones, and the ages for normally acquiring them, are given below. If a child does not acquire the skill by the age shown in parentheses, there is some cause for concern.

- Sits well unsupported—6 months (8–10 months)
- Babbles—6 months (8 months)
- Crawls—9 months (12 months)
- Finger feeds, holds bottle—9 months (12 months)
- Walks alone—12 months (15–18 months)
- Uses one or two words other than dada/mama—12 months (15 months)
- Walks up and down steps—24 months (24–36 months)
- Turns pages in books; removes shoes and socks—24 months (30 months)

Children do not consistently favor one hand over the other before 12–18 months, and doing so may be a sign that the child has difficulty using the other hand. This same preference for one side of the body may show up as asymmetric crawling or, later on, favoring one leg while climbing stairs.

It must be remembered that children normally progress at somewhat different rates, and slow beginning accomplishment is often followed by normal development. Other causes for developmental delay—some benign, some serious—should be excluded before considering CP as the answer. CP is nonprogressive, so continued loss of previously acquired milestones indicates that CP is not the cause of the problem.

No one test is diagnostic for CP, but certain factors increase suspicion. The Apgar score measures a baby's condition immediately after birth. Babies that have low Apgar scores are at increased risk for CP. Presence of abnormal muscle tone or movements may indicate CP, as may the persistence of infantile reflexes. Imaging of the brain using ultrasound, x rays, MRI, and/or CT scans may reveal a structural anomaly. Some brain lesions associated with CP include scarring, cysts, expansion of the cerebral ventricles (**hydrocephalus**), periventricular leukomalacia (an abnormality of the area surrounding the ventricles), areas of dead tissue (necrosis), and evidence

of an intracerebral hemorrhage or blood clot. Blood and urine biochemical tests, as well as genetic tests, may be used to rule out other possible causes, including muscle and peripheral nerve diseases, mitochondrial and metabolic diseases, and other inherited disorders. Evaluations by a pediatric developmental specialist and a geneticist may be of benefit.

Cerebral palsy cannot be cured, but many of the disabilities it causes can be managed through planning and timely care. Treatment for a child with CP depends on the severity, nature, and location of the primary muscular symptoms, as well as any associated problems that might be present. Optimal care of a child with mild CP may involve regular interaction with only a physical therapist and occupational therapist, whereas care for a more severely affected child may include visits to multiple medical specialists throughout life. With proper treatment and an effective plan, most people with CP can lead productive, happy lives.

Therapy

Spasticity, muscle weakness, coordination, ataxia, and scoliosis are all significant impairments that affect the posture and mobility of a person with CP. Physical and occupational therapists work with the patient and the family to maximize the ability to move affected limbs, develop normal motor patterns, and maintain posture. Assistive technology, such as wheelchairs, walkers, shoe inserts, crutches, and braces, are often required. A speech therapist and high-tech aids such as computer-controlled communication devices, can make a tremendous difference in the life of those who have speech impairments.

Medications

Before fixed contractures develop, muscle-relaxant drugs such as diazepam (Valium), dantrolene (Dantrium), and baclofen (Lioresal) may be prescribed. Botulinum toxin (Botox), a newer and highly effective treatment, is injected directly into the affected muscles. Alcohol or phenol injections into the nerve controlling the muscle are another option. Multiple medications are available to control seizures, and athetosis can be treated using medications such as trihexyphenidyl HCl (Artane) and benztropine (Cogentin).

Surgery

Fixed contractures are usually treated with either serial casting or surgery. The most commonly used surgical procedures are tenotomy, tendon transfer, and dorsal rhizotomy. In tenotomy, tendons of the affected muscle are cut and the limb is cast in a more normal position while the tendon regrows. Alternatively, tendon transfer involves cutting and reattaching a tendon at a different point on the bone to enhance the length and function of the muscle. A neurosurgeon performing dorsal rhizotomy carefully cuts selected nerve roots in the spinal cord to prevent them from stimulating the spastic muscles. Neurosurgical techniques in the brain such as implanting tiny electrodes directly into the cerebellum, or cutting a portion of the hypothalamus, have very specific uses and have had mixed results.

This nurse is taking a girl with cerebral palsy for a walk in her motorized wheelchair. Due to poor muscle control and coordination, many patients will require some form of assistive device. *(Photo Researchers, Inc.)*

Education

Parents of a child newly diagnosed with CP are not likely to have the necessary expertise to coordinate the full range of care their child will need. Although knowledgeable and caring medical professionals are indispensable for developing a care plan, a potentially more important source of information and advice is other par-

ents who have dealt with the same set of difficulties. Support groups for parents of children with CP can be significant sources of both practical advice and emotional support. Many cities have support groups that can be located through the United Cerebral Palsy Association, and most large medical centers have special multidisciplinary clinics for children with developmental disorders.

Prognosis

Cerebral palsy can affect every stage of maturation, from childhood through adolescence to adulthood. At each stage, those with CP, along with their caregivers, must strive to achieve and maintain the fullest range of experiences and education consistent with their abilities. The advice and intervention of various professionals remains crucial for many people with CP. Although CP itself is not considered a terminal disorder, it can affect a person's lifespan by increasing the risk for certain medical problems. People with mild cerebral palsy may have near-normal life spans, but the lifespan of those with more severe forms may be shortened. However, over 90% of infants with CP survive into adulthood.

The cause of most cases of CP remains unknown, but it has become clear in recent years that birth difficulties are not to blame in most cases. Rather, developmental problems before birth, usually unknown and generally undiagnosable, are responsible for most cases. The rate of survival for preterm infants has leveled off in recent years, and methods to improve the long-term health of these at-risk babies are now being sought. Current research is also focusing on the possible benefits of recognizing and treating coagulopathies and inflammatory disorders in the prenatal and perinatal periods. The use of magnesium sulfate in pregnant women with preeclampsia or threatened preterm delivery may reduce the risk of CP in very preterm infants. Finally, the risk of CP can be decreased through good maternal nutrition, avoidance of drugs and alcohol during pregnancy, and prevention or prompt treatment of infections.

Resources

BOOKS

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Pimm, Paul. *Living With Cerebral Palsy.* Austin, TX: Raintree Steck-Vaughn Publishers, 2000.

Pincus, Dion. *Everything You Need to Know About Cerebral Palsy.* New York: Rosen Publishing Group, Inc., 2000

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Seppa, Nathan. "Infections may underlie cerebral palsy." *Science News* 154 (October 17, 1998): 244.

Stephenson, Joan. "Cerebral Palsy Clues." *The Journal of the American Medical Association* 280 (21 October 1998): 1298.

ORGANIZATIONS

Epilepsy Foundation of America. 4351 Garden City Dr., Suite 406, Landover, MD 20785-2267. (301) 459-3700 or (800) 332-1000. <http://www.epilepsyfoundation.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Easter Seal Society. 230 W. Monroe St., Suite 1800, Chicago, IL 60606-4802. (312) 726-6200 or (800) 221-6827. <http://www.easter-seals.org>.

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. <http://www.nsgc.org/GeneticCounselingYou.asp>.

United Cerebral Palsy Association, Inc. (UCP). 1660 L St. NW, Suite 700, Washington, DC 20036-5602. (202)776-0406 or (800)872-5827. <http://www.ucpa.org>.

WEBSITES

"Cerebral Palsy Information Page." *National Institute of Neurological Disorders and Stroke.* <http://www.ninds.nih.gov/health_and_medical/pubs/cerebral_palsy.htm>

"Cerebral Palsy: Hope Through Research." *National Institute of Neurological Disorders and Stroke.* <http://www.ninds.nih.gov/health_and_medical/pubs/cerebral_palsyhtr.htm>

Scott J. Polzin, MS

Cerebral sclerosis *see* **Adrenoleukodystrophy (ALD)**

Cerebrohepatorenal syndrome *see* **Zellweger syndrome**

CFC syndrome *see* **Cardiofaciocutaneous syndrome**

Charcot-Marie-Tooth disease

Definition

Charcot-Marie-Tooth disease (CMT) is the name of a group of inherited disorders of the nerves in the peripheral nervous system (nerves throughout the body that communicate motor and sensory information to and from the spinal cord) causing weakness and loss of sensation in the limbs.

Description

CMT is named for the three neurologists who first described the condition in the late 1800s. It is also known as hereditary motor and sensory neuropathy and is sometimes called peroneal muscular atrophy, referring to the muscles in the leg that are often affected. The age of onset of CMT can vary anywhere from young childhood to the 50s or 60s. Symptoms typically begin by the age of 20. For reasons yet unknown, the severity in symptoms can also vary greatly, even among members of the same family.

Although CMT has been described for many years, it is only since the early 1990s that the genetic cause of many types of CMT have become known. Therefore, knowledge about CMT has increased dramatically within a short time.

The peripheral nerves

CMT affects the peripheral nerves, those groups of nerve cells carrying information to and from the spinal cord and decreases their ability to carry motor commands to muscles, especially those furthest from the spinal cord located in the feet and hands. As a result, the muscles connected to these nerves eventually weaken. CMT also affects the sensory nerves that carry information from the limbs to the brain. Therefore, people with CMT also have sensory loss. This causes symptoms such as not being able to tell if something is hot or cold or difficulties with balance.

There are two parts of the nerve that can be affected in CMT. A nerve can be likened to an electrical wire, in which the wire part is the axon of the nerve and the insulation surrounding it is the myelin sheath. The job of the myelin is to help messages travel very fast through the nerves. CMT is usually classified depending on which part of the nerve is affected. People who have problems with the myelin have CMT type 1 and people who have abnormalities of the axon have CMT type 2.

Specialized testing of the nerves, called nerve conduction testing (NCV), can be performed to determine if a person has CMT1 or CMT2. These tests measure the speed at which messages travel through the nerves. In CMT1, the messages move too slow, but in CMT2 the messages travel at the normal speed.

Genetic profile

CMT is caused by changes (mutations) in any one of a number of genes that carry the instructions to make the peripheral nerves. Genes contain the instructions for how the body grows and develops before and after a person is born. There are probably at least 15 different genes that can cause CMT. However, as of early 2001, many have not yet been identified.

CMT types 1 and 2 can be broken down into subtypes based upon the **gene** that is causing CMT. The subtypes are labeled by letters. So there is CMT1A, CMT1B, etc. Therefore, the gene with a mutation that causes CMT1A is different from that which causes CMT1B.

Types of CMT

CMT1A

The most common type of CMT is called CMT1A. It is caused by a mutation in a gene called peripheral myelin protein 22 (PMP22) located on chromosome 17. The job of this gene is to make a protein (PMP22) that makes up part of the myelin. In most people who have CMT, the mutation that causes the condition is a duplication (doubling) of the PMP22 gene. Instead of having two copies of the PMP22 gene (one on each chromosome), there are three copies. It is not known how this extra copy of the PMP22 gene causes the observed symptoms. A small percentage of people with CMT1A do not have a duplication of the PMP22 gene, but rather have a point mutation in the gene. A point mutation is like a typo in the gene that causes it to work incorrectly.

Hereditary neuropathy with liability to pressure palsies (HNPP)

HNPP is a condition that is also caused by a mutation in the PMP22 gene. The mutation is a deletion, resulting in only one copy of the PMP22 gene instead of two. People who have HNPP may have some of the signs of CMT. However, they also have episodes where they develop weakness and problems with sensation after compression of certain pressure points such as the elbows or knee. Often, these symptoms will resolve after a few days or weeks, but sometimes they are permanent.

CMT1B

Another type of CMT, called CMT1B, is caused by a mutation in a gene called myelin protein zero (MPZ)

located on chromosome 1. The job of this gene is to make the layers of myelin stick together as they are wrapped around the axon. The mutations in this gene are point mutations because they involve a change (either deletion, substitution, or insertion) at one specific component of a gene.

CMTX

Another type of CMT, called CMTX, is usually considered a subtype of CMT1 because it affects the myelin, but it has a different type of **inheritance** than type 1 or type 2. In CMTX, the CMT causing gene is located on the X chromosome and is called connexin 32 (Cx32). The job of this gene is to code for a class of protein called connexins that form tunnels between the layers of myelin.

CMT2

There are at least five different genes that can cause CMT type 2. Therefore, CMT2 has subtypes A, B, C, D and E. As of early 2001, scientists have narrowed in on the location of most of the CMT2 causing genes. However, the specific genes and the mutations have not yet been found for most types. Very recently, the gene for CMT2E has been found. The gene is called neurofilament-light (NF-L). Because it has just been discovered, not much is known about how mutations in this gene cause CMT.

CMT3

In the past a condition called Dejerine-Sottas disease was referred to as CMT3. This is a severe type of CMT in which symptoms begin in infancy or early childhood. It is now known that this is not a separate type of CMT and in fact people who have onset in infancy or early childhood often have mutations in the PMP22 or MPZ genes.

CMT4

CMT4 is a rare type of CMT in which the nerve conduction tests have slow response results. However, it is classified differently from CMT1 because it is passed through families by a different pattern of inheritance. There are five different subtypes and each has only been described in a few families. The symptoms in CMT4 are often severe and other symptoms such as deafness may be present. There are three different genes that have been associated with CMT4 as of early 2001. They are called MTMR2, EGR2, and NDRG1. More research is required to understand how mutations in these genes cause CMT.

Inheritance

Autosomal dominant inheritance

CMT1A and 1B, HNPP, and all of the subtypes of CMT2 have autosomal dominant inheritance. Autosomal refers to the first 22 pairs of **chromosomes** that are the same in males and females. Therefore, males and females are affected equally in these types. In a dominant condition, only one gene of a pair needs to have a mutation in order for a person to have symptoms of the condition. Therefore, anyone who has these types has a 50%, or one in two, chance of passing CMT on to each of their children. This chance is the same for each pregnancy and does not change based on previous children.

X-linked inheritance

CMTX has X-linked inheritance. Since males only have one X chromosome, they only have one copy of the Cx32 gene. Thus, when a male has a mutation in his Cx32 gene, he will have CMT. However, females have two X chromosomes and therefore have two copies of the Cx32 gene. If they have a mutation in one copy of their Cx32 genes, they will only have mild to moderate symptoms of CMT that may go unnoticed. This is because their normal copy of the Cx32 gene produces sufficient amounts of myelin.

Females pass on one or the other of their X chromosomes to their children—sons or daughters. If a woman with a Cx32 mutation passes her normal X chromosome, she will have an unaffected son or daughter who will not pass CMT on to their children. If the woman passes the chromosome with Cx32 mutation on she will have an affected son or daughter, although the daughter will be mildly affected or have no symptoms. Therefore, a woman with a Cx32 mutation has a 50%, or a one in two chance of passing the mutation to her children: a son will be affected, and a daughter may only have mild symptoms.

When males pass on an X chromosome, they have a daughter. When they pass on a Y chromosome, they have a son. Since the Cx32 mutation is on the X chromosome, a man with CMTX will always pass the Cx32 mutation on to his daughters. However, when he has a son, he passes on the Y chromosome, and therefore the son will not be affected. Therefore, an affected male passes the Cx32 **gene mutation** on to all of his daughters, but to none of his sons.

Autosomal recessive inheritance

CMT4 has autosomal recessive inheritance. Males and females are equally affected. In order for a person to have CMT4, they must have a mutation in both of their

CMT causing genes—one inherited from each parent. The parents of an affected person are called carriers. They have one normal copy of the gene and one copy with a mutation. Carriers do not have symptoms of CMT. Two carrier parents have a 25%, or one in four chance of passing CMT on to each of their children.

Demographics

CMT has been diagnosed in people from all over the world. It occurs in approximately one in 2,500 people, which is about the same incidence as multiple sclerosis. It is the most common type of inherited neurologic condition.

Signs and symptoms

The onset of symptoms is highly variable, even among members of the same family. Symptoms usually progress very slowly over a person's lifetime. The main problems caused by CMT are weakness and loss of sensation mainly in the feet and hands. The first symptoms are usually problems with the feet such as high arches and problems with walking and running. Tripping while walking and sprained ankles are common. Muscle loss in the feet and calves leads to "foot drop" where the foot does not lift high enough off the ground when walking. Complaints of cold legs are common, as are cramps in the legs, especially after exercise.

In many people, the fingers and hands eventually become affected. Muscle loss in the hands can make fine movements such as working buttons and zippers difficult. Some patients develop tremor in the upper limbs. Loss of sensation can cause problems such as numbness and the inability to feel if something is hot or cold. Most people with CMT remain able to walk throughout their lives.

Diagnosis

Diagnosis of CMT begins with a careful neurological exam to determine the extent and distribution of weakness. A thorough family history should be taken at this time to determine if other people in the family are affected. Testing may be also performed to rule out other causes of neuropathy.

A nerve conduction velocity test should be performed to measure how fast impulses travel through the nerves. This test may show characteristic features of CMT, but it is not diagnostic of CMT. Nerve conduction testing may be combined with electromyography (EMG), an electrical test of the muscles.

A nerve biopsy (removal of a small piece of the nerve) may be performed to look for changes characteristic of CMT. However, this testing is not diagnostic of CMT and is usually not necessary for making a diagnosis.

KEY TERMS

Axon—Skinny, wire-like extension of nerve cells.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system, which help them conduct impulses more quickly.

Nerve conduction testing—Procedure that measures the speed at which impulses move through the nerves.

Neuropathy—A condition caused by nerve damage. Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

Peripheral nerves—Nerves throughout the body that carry information to and from the spinal cord.

Definitive diagnosis of CMT is made only by **genetic testing**, usually performed by drawing a small amount of blood. As of early 2001, testing is available to detect mutations in PMP22, MPZ, Cx32, and EGR2. However, research is progressing rapidly and new testing is often made available every few months. All affected members of a family have the same type of CMT. Therefore once a mutation is found in one affected member, it is possible to test other members who may have symptoms or are at risk of developing CMT.

Prenatal diagnosis

Testing during pregnancy to determine whether an unborn child is affected is possible if genetic testing in a family has identified a specific CMT-causing mutation. This can be done after 10-12 weeks of pregnancy using a procedure called chorionic villus sampling (CVS). CVS involves removing a tiny piece of the placenta and examining the cells. Testing can also be done by **amniocentesis** after 16 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it, and those who are interested in learning more should check with their doctor or genetic counselor. Couples interested in these options should obtain **genetic counseling** to carefully explore all of the benefits and limitations of these procedures.

Treatment and management

There is no cure for CMT. However, physical and occupational therapy are an important part of CMT treat-

ment. Physical therapy is used to preserve range of motion and minimize deformity caused by muscle shortening, or contracture. Braces are sometimes used to improve control of the lower extremities that can help tremendously with balance. After wearing braces, people often find that they have more energy because they are using less energy to focus on their walking. Occupational therapy is used to provide devices and techniques that can assist tasks such as dressing, feeding, writing, and other routine activities of daily life. Voice-activated software can also help people who have problems with fine motor control.

It is very important that people with CMT avoid injury that causes them to be immobile for long periods of time. It is often difficult for people with CMT to return to their original strength after injury.

There is a long list of medications that should be avoided if possible by people diagnosed with CMT such as hydralazine (Apresoline), megadoses of vitamin A, B_6, and D, Taxol, and large intravenous doses of penicillin. Complete lists are available from the CMT support groups. People considering taking any of these medications should weigh the risks and benefits with their physician.

Prognosis

The symptoms of CMT usually progress slowly over many years, but do not usually shorten life expectancy. The majority of people with CMT do not need to use a wheelchair during their lifetime. Most people with CMT are able to lead full and productive lives despite their physical challenges.

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ORGANIZATIONS

Charcot Marie Tooth Association (CMTA). 2700 Chestnut Parkway, Chester, PA 19013. (610) 499-9264 or (800) 606-CMTA. Fax: (610) 499-9267. cmtassoc@aol.com. <www.charcot-marie-tooth.org>.

CMT International. Attn: Linda Crabtree, 1 Springbank Dr. St. Catherine's, ONT L2S2K1. Canada (905) 687-3630. <www.cmtint.org>.

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

Neuropathy Association. 60 E. 42nd St. Suite 942, New York, NY 10165. (212) 692-0662. <www.neuropathy.org>.

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Karen M. Krajewski, MS, CGC

CHARGE syndrome

Definition

CHARGE syndrome, also known as CHARGE association, is a group of major and minor malformations that have been observed to occur together more frequently than expected by chance. The name of the syndrome is an acronym for some of its features, and each letter stands for the following conditions:

- C—Coloboma and/or cranial nerves
- H—Heart defects
- A—Atresia choanae,
- R—Retarded growth and development
- G—Genital anomalies
- E—Ear anomalies

While these features have classically been used for identification of affected individuals, many other malformations and medical problems have been observed to occur with this syndrome.

Description

CHARGE syndrome was first described in 1979 as an association of multiple congenital anomalies, all of which included choanal atresia, meaning the blocking of the choanae, the passages from the back of the nose to the throat which allow breathing through the nose. Soon after, several other papers were published describing similar patients who all had both choanal atresia and **coloboma**, that is a cleft or failure to close off the eyeball. It was in 1981 that the CHARGE acronym was proposed to describe the features of the condition. Due to the

large number of patients described since 1979, many physicians now regard CHARGE association as a recognizable syndrome. However, the cause for the condition remains unclear. It is believed that perhaps a new dominant change in a **gene** is the cause for many cases. There have been a few familial cases but most cases are sporadic. Crucial development of the choanoa, heart, ear and other organs occurs 35-45 days after conception and any disruption in development during this time is believed to lead to many of the features of the syndrome.

Infants with CHARGE syndrome generally have difficulty with feeding and most of those affected have mental retardation. About half die during the first year of life from respiratory insufficiency, central nervous system (CNS) malformations, and bilateral choanal atresia.

KEY TERMS

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Germ line mosaicism—A rare event that occurs when one parent carries an altered gene mutation that affects his or her germ line cells (either the egg or sperm cells) but is not found in the somatic (body) cells.

Phenotype—The physical expression of an individuals genes.

Variable expressivity—Differences in the symptoms of a disorder between family members with the same genetic disease.

Genetic profile

Most cases of CHARGE syndrome are sporadic, meaning that they occur in a random or isolated way. However, reports of parent-to-child transmission of the condition indicate an autosomal dominant type of **inheritance**. There have also been cases in which a parent with one or two features of CHARGE had a child with enough features to fit the diagnosis. These families may demonstrate variable expressivity of a dominant gene. In addition, there have been a few cases of siblings affected, suggesting the possible presence of a mixture of cell types (germ line mosaicism) in a parent for a dominant mutation. Therefore, the recurrence risk for healthy parents of an affected child would be low, but not negligible.

Twin studies are often used to determine if the occurrence of a condition has a strong genetic component. One such study compared a pair of monozygotic twins, meaning identical twins resulting from a single zygote (fertilized egg that leads to the birth of two individuals), who were both affected with CHARGE syndrome and a pair of dizygotic twins, meaning twins that result from fertilization of two different eggs, of whom only one had the syndrome. Since monozygotic twins are roughly 100% genetically identical, this supports the idea that there is a strong genetic factor involved in CHARGE syndrome. Other interesting observations include slightly increased paternal age in sporadic cases. The mean paternal age in one study was 34 years as opposed to 30 years in a control group. Increased paternal age has been known to be associated with the increased occurrence of new dominant mutations in offspring.

Several patients with various chromosome defects have been diagnosed with CHARGE syndrome, again pointing to genetic factors as a cause. These cases of **chromosomal abnormalities** point to particular genes that should be further studied. In addition, some patients with CHARGE syndrome also have features of another condition called Di George sequence which involves an immune deficiency, characteristic heart abnormalities and distinct craniofacial features. Many patients with Di George sequence have a missing chromosome 22q11. Therefore, newly diagnosed cases of CHARGE syndrome should have chromosome studies as well as molecular testing.

Demographics

The incidence of CHARGE syndrome is approximately one in 10,000. However, this is probably an underestimate of the true number of people affected. The incidence is likely to increase as the diagnostic features of the condition are refined and milder cases are diagnosed. CHARGE syndrome affects males more seriously than females, resulting in a higher number of females who survive. The cause of this is unclear. The syndrome has not been reported more often in any particular race or geographic area.

Signs and symptoms

CHARGE syndrome is believed to be caused by a disruption of fetal growth during the first three months of pregnancy and affecting many different organ systems undergoing development at that time.

Choanal atresia

Choanal atresia, the narrowing passages from the back of the nose to the throat, may occur on one or both sides (bilateral) of the nose. This condition usually leads to breathing difficulties shortly after birth. Bilateral choanal atresia may result in early death and surgery is

often required to open up the nasal passages. Choanal atresia is also often accompanied by hearing loss. Since bilateral choanal atresia is rare, CHARGE syndrome should be considered in all babies with this finding. Fifty to sixty percent of children diagnosed with CHARGE syndrome have choanal atresia.

Heart abnormalities

Seventy-five to eighty-five percent of children with CHARGE syndrome have heart abnormalities. Many are minor defects, but many require treatment or surgery. Some of the heart abnormalities seen in CHARGE syndrome are very serious (e.g. tetralogy of Fallot) and life threatening. Every child with a diagnosis of CHARGE syndrome should have an echocardiogram, a test that uses sound waves to produce pictures of the heart.

Coloboma and eye abnormalities

A coloboma is a cleft or failure to close off the eyeball properly. This can result in a keyhole shaped pupil or abnormalities in the retina of the eye or its optic nerve. The condition is visible during an eye exam. Colobomas may or may not cause visual changes. About 80% of children with CHARGE syndrome have colobomas and the effect on vision varies from mild to severe. Other eye abnormalities include microphthalmia (small eye slits) or anophthalmia (no eyes). Consistent eye examinations are recommended for children diagnosed with the syndrome.

Ear abnormalities and deafness

At least 90% of patients with CHARGE syndrome have either external ear anomalies or hearing loss. The most common external ear anomalies include low-set ears, asymmetric ears, or small or absent ear lobes. The degree of hearing loss varies from mild to severe. It is important for all patients to have regular hearing exams over time so that changes in sound perception can be detected. Hearing aids are used as soon as hearing loss is detected. Some patients require corrective surgery of the outer ear, so that a hearing aid can be worn. Children with CHARGE syndrome often develop ear infections and this can affect hearing over time as well.

Cranial nerve defects

Defects related to the formation of the cranial nerves during fetal development are common in patients with CHARGE syndrome. The defects include anosmia (inability to smell), facial palsy, hearing loss, and swallowing difficulty. Facial palsy is the inability to sense or control movement of part of the face. This usually occurs on one side of the face, which, in affected individuals, results in a characteristic asymmetric and expressionless look. Swallowing problems can also occur along with several different defects in the formation of the throat.

Facial features

The facial features of CHARGE syndrome are considered minor diagnostic signs because they are not as obvious as the facial features of other genetic syndromes. However, many patients have facial asymmetry, a small and underdeveloped jaw, a broad forehead, square face, arched eyebrows, and external ear malformations.

Growth and developmental delays

Most babies with CHARGE syndrome have normal length and weight at birth. Difficulty with feeding and the presence of other malformations often leads to weight loss, so that these babies usually weigh less for their age. Teenagers are also often shorter than average due to a delay in the onset of puberty. In a small number of patients, growth delay is due to a lack of growth hormone.

There are serious delays in motor development of children with CHARGE syndrome as well. Many children have low muscle tone and difficulty with balance that leads to delays in walking. Physical therapy is often helpful. Most children with CHARGE syndrome are classified as mentally retarded. However, successful treatment of other features of the condition can improve learning potential. Therefore, assessments made before other medical problems are addressed are often more pessimistic than later exams.

Urogenital abnormalities

Most obvious in males, underdevelopment of the genitals occurs in at least half of the male patients diagnosed with CHARGE syndrome and in some females as well. Abnormalities of genitalia in males include an underdeveloped penis (micropenis or microphallus) and testicles that fail to descend to the scrotum (cryptorchidism). In females, there may be overgrowth or underdevelopment of the labia or clitoris. Information concerning the fertility of patients is not available. About 25% of children have renal abnormalities that may lead to repeated infections. A renal ultrasound is indicated in children with the syndrome.

Central nervous system anomalies

In one series of tested patients, CNS anomalies were noted in 83% of the patients who underwent imaging tests that produce pictures of the brain such as MRI, CT

scan, and ultrasound, or after autopsy. The CNS anomalies included diminution of the size of the brain (cerebral atrophy), asymmetry, and midline defects such as partial development (e.g. agenesis of the corpus callosum). In addition, brain stem dysfunction has also been observed after birth, a disorder that can cause respiratory and swallowing problems. These findings were associated with a poor prognosis.

Associated anomalies

Many other features have been reported in patients with CHARGE syndrome. Some of these include a cleft lip and/or palate, dental anomalies, absence of the thymus and parathyroid glands that leads to immunodeficiency (the inability of the body to produce a normal immune response), seizures, abormally low levels of calcium (hypocalcaemia) or sugar (hypoglycemia) in the body, obstruction of the anal opening (imperforate anus), groin hernias, curvature of the spine (**scoliosis**), skeletal anomalies, body temperature regulation problems and umbilical hernias.

Diagnosis

Since there is currently no genetic test available for CHARGE syndrome, the diagnosis is based on clinical features. There is disagreement about the conditions required for diagnosis. Some suggest that one major malformation plus four of the other features suggested by the CHARGE acronym are sufficient. Others suggest that four major characteristics or three major characteristics plus three minor characteristics are sufficient for diagnosis.

The Charge Syndrome Foundation defines a specific set of birth defects and most common features to diagnose CHARGE syndrome. These major features include: choanal atresia, coloboma, cranial nerve abnormalities and conditions, such as swallowing problems (due to cranial nerve IX/X defects), facial palsy (due to cranial nerve VII defects), hearing loss (due to cranial nerve VIII defects), heart defects, and retardation of growth and development.

Other minor features have also been reported that are either less common or less specific to CHARGE syndrome. These include genital abnormalities, cleft lip and/or palate, tracheoesophageal fistula and facial distortions.

Diagnosis of CHARGE syndrome before birth has not yet been reported. The condition may be suspected when a prenatal ultrasound reveals fetal growth restriction, CNS malformations, heart defects, and urinary tract malformations. In one series, 37.5% of patients diagnosed with CHARGE were noted to have an abnormal feature noted on ultrasound.

There are several other conditions that include signs similar to CHARGE syndrome. These include VACTERL association (for vertebral, anal, cardiac, tracheoesophageal, renal and limb abnormalities, velocardiofacial (VCF) syndrome (**deletion 22q11 syndrome**), and prenatal retinoic acid exposure (**Accutane embryopathy**).

Treatment and management

Treatment for CHARGE syndrome is specific to the features present in each child. Choanal atresia can be treated with dilatations of the choanoa or nasal passages. Heart defects may require surgery. Children with CHARGE syndrome should get ophthalmology and hearing screens every six months. Plastic surgery is sometimes needed for corrections of ear malformations or facial asymmetry. Medications are needed when seizures are present and growth hormone is sometimes taken for growth delay or underdeveloped genitalia.

A developmental evaluation and a plan for special education are required. Patients with CHARGE syndrome who have both hearing and vision difficulty should receive care from childhood educators experienced in dual sensory impairment. Once these children establish a system of mobility and communication, the degree of developmental retardation may improve. Lengthy hospital stays for children with CHARGE syndrome may limit the ability of specialists to work with the child in the early months. Once major hospitalizations are completed, development may improve as the result of regular care by the appropriate child specialists. Other learning problems have been noted and should also be addressed if present. These include attention deficit disorder, **autism**, and obsessive-compulsive disorder. Parents are often in the position of coordinating the many components of special education for their children. The national and international support groups for CHARGE syndrome are able to provide information and assistance in this area.

Prognosis

It has been noted in several studies that about half of patients diagnosed with CHARGE syndrome die from complications of the condition. One study suggests that 40% of those die after birth. Factors that appear to influence survival include the presence of CNS malformations, bilateral choanal atresia, TE fistula, and male gender. Heart abnormalities and brain stem dysfunctions were not found to be related to poor prognosis. Significant hospitalizations are needed for most children with CHARGE syndrome.

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ORGANIZATIONS

CHARGE Family Support Group. 82 Gwendolen Ave., London, E13 ORD. UK 020-8552-6961. <http://www.widerworld.co.uk/charge>.

CHARGE Syndrome Foundation. 2004 Parkade Blvd., Columbia, MO 65202-3121. (800) 442-7604. <http://www.chargesyndrome.org>.

Sonja Rene Eubanks, MS, CGC

Chediak-Higashi syndrome

Definition

Chediak-Higashi syndrome (CHS) is a very rare disease that affects almost every organ in the body. It is an autosomal recessive disease that results from an abnormality in lysosomes (a sac-like container of enzymes) that travel within cells. The problems that occur with this disease are quite varied and present in two stages.

Description

Chediak-Higashi syndrome was named for the two scientists who, in 1957, further detailed the disorder first described by a Cuban doctor in 1943. The disease progresses through two different stages: the "stable phase" and the "accelerated phase." This rare disease has both classic external signs and distinct cellular problems that always result in a fatal outcome.

Affected individuals have many kinds of immune system problems, making them more likely to get infections and cell proliferation problems. People with CHS have a lowered ability to target infectious organisms, and once their immune cells do become involved, they have a harder time killing the infectious organisms.

Affected individuals also have problems with their melanocytes, the cells that produce melanin, the compound that gives skin, hair, and eyes their color. Often, this can result in signs of **albinism** (lack of color in the skin, hair, and eyes).

Genetic profile

Chediak-Higashi is an autosomal recessive disease, which requires both parents to be carriers of altered, or mutated, genes. CHS often occurs in families with a history of marrying close relatives. Based on genetic mapping that was first done in a mouse model of Chediak-Higashi syndrome, a mutated **gene** found on chromosome 1q is thought to be the cause of the disease. This gene is called LYST.

Genetic tests of many different affected people with the disease have revealed strong signs of allelic variability (different mutations in the same gene). Some evidence suggests that the allelic variability accounts for the many different presentations of the disease, such as differing age of presentation, differences in the severity of symptoms, and different progression into the second stage of the disease.

Demographics

About 200 cases of CHS have been described in the world's literature. It is seen in the same number of males and females. Often there is a history of intermarriage.

Signs and symptoms

People with Chediak-Higashi syndrome will often have many different clinical problems such as recurrent bacterial infections without clear causes, fevers that cannot be explained, severe gingivitis (gum disease), peripheral and cranial neuropathies, vision problems, lack of coordination, weakness, easy bruising, and loss of coloring (hypopigmentation) of the hair, skin and eyes.

During the accelerated phase, affected people may show signs of enlargement of the liver and spleen (hepatosplenomegaly), low blood platelet counts (thrombocytopenia), low counts of a certain white blood cell group (neutropenia), and low red blood cell counts (anemia). Abnormal cells can cause bone marrow infiltration and suppression, and this may lower blood counts further, making affected individuals even more susceptible to infections. The transformation to the accelerated phase of this disease tends to occur in the first or second decade of life.

Diagnosis

Diagnosis of CHS is based on microscopic examination of an affected person's blood, and possibly their

bone marrow. Examiners look for giant lysosomal granules, which are abnormal groups of cellular sections inside certain white blood cells. At present, the carrier state of Chediak-Higashi syndrome cannot be diagnosed. Prenatal testing has been done using fetal blood samples and cells taken from the amniotic fluid around the fetus. **Genetic testing** is not yet available.

Since this disorder is passed on in an autosomal recessive fashion, parents who have one affected child should have **genetic counseling** before future pregnancies. With each pregnancy these parents have a 25% chance of having another affected child.

Treatment and management

The treatment of Chediak-Higashi syndrome differs based on the stage of the illness. During the stable phase, treatment is aimed at controlling infectious problems. Prophylactic antibiotics can be given to affected individuals to reduce the risk of contracting the more common infections. Some evidence suggests that treatment with high doses of ascorbic acid (vitamin C) can help improve people clinically as well as improve immune system cell functions in laboratory tests.

During the accelerated phase of this disease, treatment is very difficult. Some affected people have done well with chemotherapy that is aimed at the abnormally growing cells. Some literature has claimed benefits from bone marrow transplants. Also, some literature has indicated that the vaccination of affected individuals against specific viruses may help prevent transformation of the disease from the stable phase into the accelerated phase.

Prognosis

Most affected people described in the medical literature died of infections during the accelerated phase of CHS. This occurred during their youth or teenage years. There are some reports of affected people living into their 30s.

Resources

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Benjamin M. Greenberg

KEY TERMS

Allelic variability—Different mutations in the same gene, producing like outcomes.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Melanin—Pigments normally produced by the body that give color to the skin and hair.

Melanocyte—A cell that can produce melanin.

Chiari malformation *see* **Arnold-Chiari malformation**

Chondroectodermal dysplasia *see* **Ellis-Van Creveld syndrome**

Chondrosarcoma

Definition

Chondrosarcoma is a malignant tumor that produces a special type of connective tissue called cartilage. Malignant tumors have cells that have the ability to invade and are characterized by uncontrolled growth.

Description

Cartilage is a type of connective tissue that acts as a resistant surface. Cells called chondrocytes produce cartilage. Chondrosarcoma is a malignant growth arising in chondrocytes. There are two types of chondrosarcomas, either primary or secondary. Primary chondrosarcomas arise in areas of previously normal bone that are derived from cartilage. Secondary chondrosarcomas are lesions produced from pre-existing cartilage lesions. The chondrosarcoma tumors either produce enlargement or erosion of the area involved. The lesion is classified further as to where the lesion occurs and the grade of the lesion. It is graded from 1 (low-grade) to 3 (high-grade). This classification states that the higher the grade of the tumor, the higher the increased atypia, or abnormal cell growth.

Two non-cancerous diseases, Maffuci disease and Ollier disease, are similar to chondrosarcoma. Ollier disease, also known as enchondromatosis or dyschondroplasia, is a disorder affecting the growth plates of bone where new bone is deposited. The cartilage laid down is

KEY TERMS

Atypia—Lacking uniformity.

Cartilage—Supportive connective tissue which cushions bone at the joints or which connects muscle to bone.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Curettage—A surgical scraping or cleaning.

Enchondromas—Benign cartilaginous tumors arising in the cavity of bone. They have the possibility of causing lytic destruction within the bone.

Excision—Surgical removal.

Lysis—Area of destruction.

Maffucci disease—A manifestation of Ollier disease (multiple enchondromatosis) with hemangiomas, which present as soft tissue masses.

Myxoid—Resembling mucus.

Ollier disease—Also termed multiple enchondromatosis. Excessive cartilage growth within the bone extremities that result in benign cartilaginous tumors arising in the bone cavity.

Radiolucent—Transparent to x ray or radiation. The black area on x-ray film.

Urinary urgency—An exaggerated or increased sense of needing to urinate.

not reabsorbed and masses form near the ends of the long bones such as the thigh bone (femur) and upper arm bone (humerus). Maffucci disease has the same abnormalities as Ollier disease as well as soft tissue destruction including the skin. Patients with Maffucci or Ollier disease should have bone scans every three to five years to monitor potential malignant transformations.

Genetic profile

Anomalies of **chromosomes** 5, 7, 8, and 18 and structural alterations of chromosomes 1, 12, and 15 are commonly found in patients diagnosed with chondrosarcoma. Interestingly, the **gene** for the area of normal cartilage production, type II collagen, has been found in the same regions as chondrosarcoma. Studies on the tumor suppressor gene, EXT1, have shown that changes (mutations) of this gene may also be important in the growth of chondrosarcoma.

Demographics

In 2001, an estimated 2,900 new cases of bone and joint **cancer** will be diagnosed. Primary cancer of bones accounts for less than 0.2% of all cancers. Chondrosarcoma is the second most common primary malignant bone tumor, meaning it did not originate at another site in the body. Osteosarcoma is the first most common.

There are conflicting reports as to how much more frequently men are diagnosed with chondrosarcoma than females. Findings range from twice as many males to only slightly more males than females. Chondrosarcoma occurs in people from the age of 30-70 years old, but it most commonly affects people over the age of 40. No ethnic group is affected more frequently than another.

Signs and symptoms

The signs and symptoms vary due to the type of tumor, but pain is typically the first symptom. If it is a fast growing, high grade form of chondrosarcoma, then the individual may have very severe pain. A low grade, slow growing, tumor usually has pain and swelling in the area of the tumor. If the tumor is located in the pelvis or hip area, the individual may have difficulty with urination or urinary urgency. The patient may also have the sensation of a groin pull if the tumor is in the pelvic area.

Diagnosis

Usually, chondrosarcoma is diagnosed with x ray radiography. X rays can show soft tissue calcification, where the muscles appear to be forming bone. The appearance of a soft tissue mass that has not yet calcified may also be visible. If the chondrosarcoma is secondary to another type of tumor, the chondrosarcoma may start to erode the edges of the other tumor. This is common where an enchondroma, a type of tumor within the bone shaft, is present. In this case, the chondrosarcoma produces areas of lysis, or destruction of the surrounding tissue.

Biopsy is used to determine the grade of the tumor. Grade 1 chondrosarcomas, or low-grade slow growing lesions, have a mild increase of new cell growth. Grade 3 chondrosarcomas are the opposite: they are high-grade, fast growing, and have a dramatic increase in cellular growth. The more radiolucent, or transparent to x rays, the tumor appears, the greater the chance it is a higher grade.

Other imaging tests may also be used. Computed tomography scanning, CT, is an advanced form of x ray that can also produce bone pictures and help determine how much calcification the tumor is producing. Magnetic

resonance imaging, MRI, will aid diagnosis since it can differentiate soft tissues such as muscle and fat. MRI will help determine the amount of malignant degeneration of the chondrosarcoma.

Treatment and management

The main course of therapy for chondrosarcoma is surgical removal of the tumor. The amount of surgery depends on the location and the stage of the tumor. Very low-grade tumors may be surgically removed. High-grade chondrosarcomas necessitate more radical operations where normal tissue is also removed due to the possibility of spread. If the tumor is located in an extremity such as an arm or leg, then amputation, or surgical removal of the extremity, may be necessary in order to prevent metastasis, or spread of the cancer. Chemotherapy and radiotherapy may also be used depending on the type of tumor and the area of the body affected, but are usually not effective.

Prognosis

The higher the grade of a chondrosarcoma, the more likely the tumor will spread and thus worsen the prognosis. One study found the five year survival rate of patients with grades 1, 2, and 3 to be 90%, 83%, and 43% respectively. This means that five years after the diagnosis of the tumor, 90 out of 100 people with grade 1 were still alive. On the opposite spectrum, 43 out of 100 patients with grade 3 chondrosarcoma survived five years. Therefore the survival rate is very much dependent on the stage of the tumor and also on its location. Size of the tumor is also an important factor. Tumors greater than 4 in (10 cm) are more likely to become aggressive and spread. When they do spread, or metastasize, they often migrate to the lungs and skeleton.

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Cancernet. National Cancer Institute, National Institutes of Health. NCI Public Inquiries Office, Building 31, Room 10A03, 31 Center Dr., MSC 2580, Bethesda, MD 20892-2580 USA.

American Cancer Society. Bone Cancer Resource Center. 1599 Clifton Road, NE, Atlanta, GA 30329. (800) 227-2345 or (404) 320-3333. <http://www.cancer.org/>.

WEBSITES

Bone Tumor Organization. <http://www.bonetumor.com/page39.html>.

Jason S. Schliesser, DC

Choroideremia

Definition

Choroideremia is a rare genetic disorder causing progressive eyesight loss due to the wasting away of retinal layers. It first affects the choroid and the retinal pigmented epithelium (RPE) layers and finally the photoreceptor cell layer. Atrophy (wasting) of the optic nerve is also observed in choroideremia.

Description

Formerly called tapetochoroidal dystrophy, choroideremia is a chronic form of retinal disease characterized by degeneration of the layers of the retina, which is the light-sensitive part of the eye. There are four main retinal layers: the outer neural retina, consisting of nerve cells and blood vessels; the retinal pigment epithelium (RPE); the choroid layer that contains connective eye tissue and a capillary layer (chorio capillaris); and the photoreceptor (light-sensitive) layer that contain the rods and cones, which function as detectors to process light, color and shape signals to the brain. Choroideremia is a progressive disease, meaning that the layers become affected one after the other over time.

The pigmentary changes in the RPE begin with fine spotting and continue with areas of depigmentation and increasing loss of the chorio capillaris. Chorio capillaris loss and degeneration of the larger choroidal blood vessels causes areas of bare sclera, the tough white fibrous tissue that covers the "white" of the eye. The disease begins in midperiphery of the choroid but then progresses to include the entire choroid.

Choroidal vessels provide oxygen and nutrients to both the RPE and the retina's photoreceptor cells. The RPE, which lies directly beneath the retina, supports the function of photoreceptor cells. Photoreceptor cells (rods and cones) convert light into the electrical impulses that transfer messages to the brain where "seeing" actually occurs. In the early stages of choroideremia, the choroid and the RPE begin to deteriorate. Eventually, photore-

ceptor cells also degenerate, resulting in a loss of central vision.

The age at which choroideremia first appears varies; initial symptoms (usually night blindness) may occur as early as three years of age and as late as 40 years. However, occurrence peaks between the ages of ten and 40. The visual field becomes progressively constricted, and patients usually reach legal blindness by 25 years of age. Loss of central vision usually occurs after the age of 35. However, in nearly all patients with choroideremia, visual acuity (acuteness or sharpness of vision) is well maintained until the late stages of the disease.

Genetic profile

Choroideremia is an X-linked, recessive disorder, or a condition that is transmitted on the X chromosome. Females have two X **chromosomes**; males have an X and a Y chromosome. Thus in females, the altered **gene** on one X chromosome can be masked by the normal gene on the other X chromosome. Female carriers—who may or may not be symptomatic—have a 50% chance of passing the X-linked abnormal gene to their daughters, who become carriers, and a 50% chance of passing the gene to their sons, who are then affected by the disease.

Choroideremia was the first of the retinal disorders to be mapped, the first to be cloned, and the first to have a simple protein test assigned to it. In 1991, Dr. Fran Cremers of the University of Nijmegen in the Netherlands isolated the gene believed to be responsible for choroiderermia. The gene for choroideremia was found on the Xq21 band of the X chromosome.

Although the choroideremia gene causes problems in the retina, choroid, and RPE, expression of this gene is not limited to the eyes. Choroideremia may also manifest as a generalized disorder. Choroideremia has been classified into two general types: isolated or associated.

Isolated choroideremia

In isolated choroideremia, which is the most common form of the disorder, affected individuals display only disease-related ocular symptoms.

Associated choroideremia

Although relatively rare, associated choroideremia with mental retardation occurs in patients with a deletion of part of the X chromosome, including the region called Xq21. Such a deletion may cause choroideremia with severe mental retardation or with mental retardation and congenital deafness. In these individuals, the mothers are the carriers, showing the same deletions but not the severe clinical manifestations.

Demographics

Choroideremia is believed to affect approximately one in 100,000 individuals—primarily men—although women who are carriers may exhibit mild symptoms as well. The disorder may be generally under-reported because there was no diagnostic test for choroideremia until the late 1990s.

In an area of northern Finland (the Sala region), for reasons that have yet to be determined, choroideremia has affected an unusually large number of people; about one in forty people have the disorder.

Signs and symptoms

A variety of other degenerations of the choroid may look like choroideremia. The decreased night and peripheral vision and diffuse pigmentary abnormalities seen in the early stages of the disorder are symptoms also seen in X-linked **retinitis pigmentosa** (one of a group of genetic vision disorders causing retinal degeneration). However, unlike retinitis pigmentosa, which starts in early childhood, the onset of choroideremia is variable and is rarely seen in childhood. The distinguishing feature of choroideremia is the diffuse choroidal atrophy that is uncommon in early retinitis pigmentosa.

Because the diffuse, progressive atrophy of the chorio capillaris and RPE layers begins peripherally and spreads centrally, central macular function is preserved until late in the course of the disease. **Myopia** occurs more frequently in men diagnosed with choroideremia. Although symptoms vary widely among affected individuals, men usually retain little or no useful vision beyond the age of 60.

Choroideremia is characterized by extensive abnormalities in the RPE layer. The initial symptoms include wasting of the retinal layers and choroid of the eye. The choroid (the vascular membrane located between the retina inside the eye and the sclera) contains large branched pigmented cells and prevents light rays from passing through areas of the eye outside of the pupils. Night blindness is usually the first noticeable symptom of choroideremia, usually occurring during childhood.

Degeneration of the vessels of the choroid and functional damage to the retina occur later in life and usually lead to progressive central vision field loss and eventual blindness. Small bony-like formations and scattered pigment clumps tend to accumulate in the middle portion and on the edges of the choroid. In addition, color vision is initially normal but may later evolve into tritanopia (**color blindness** in which there is an abnormality in the perception of blue).

Female carriers usually have no symptoms and have normal visual fields, normal electroretinograms (a measurement of electrical activity of the retina), and normal visual acuity. However, female carriers sometimes show abnormalities of the interior lining of the eye in the form of pigment spotting with tiny patches of RPE depigmentation. Brownish granular pigmentation and changes in the RPE and choroid may occur later. There is also some evidence to suggest that mild progression of symptoms—and even the full disease—may occur in a small number of female carriers.

Diagnosis

Although there is no treatment for choroideremia because the disorder is so rare and has received relatively little research attention, a diagnostic blood test developed by Canadian researchers allows early diagnosis of the disorder. Patients with the abnormal choroideremia gene lack a protein called Rab Escort Protein-1 (REP-1), which is involved in the lipid (any one of a group of fats or fat-like substances) modification of protein—a process called prenylation. The test uses a monoclonal antibody (an antibody of exceptional purity and specificity, derived from a single cell) to determine the presence or absence of the REP-1 protein in blood samples. The REP-1 test is unable to determine carrier status, however; the REP-1 protein is present in female carriers.

Because no biochemical abnormality has been found in choroideremia, no single laboratory test is available for diagnosis. Rather, the diagnosis is based on the typical retinal abnormalities, abnormal electroretinogram findings, the progressive course of the disorder, and the combination of typical symptoms. Family history is also helpful in diagnosing the disorder. When the diagnosis is in doubt, examination of the mother usually reveals the pigmentary changes and other retinal abnormalities typically found in carriers.

Choroideremia is one of the few retinal degenerative disorders that may be detected before birth in some cases (in women who have been found to be carriers due to family history or abnormal ophthalmologic findings). All family members with a history of choroideremia are encouraged to consult an ophthalmologist and to seek **genetic counseling**. These professionals can explain the disease and the **inheritance** risk for all family members and for future offspring.

Treatment and management

There is no treatment for choroideremia because further research is needed to understand the exact mechanism causing this progressive loss of vision. It is not known whether any external environmental factors, such as light, contribute to the progression of the disease, or if genetic factors alone are responsible for the great variability observed. However, patients diagnosed with the disorder early are better able to make decisions regarding family planning and the onset of blindness.

Assistance for individuals with choroideremia is available through low-vision aids, including optical, electronic, and computer-based devices. Personal, educational, and vocational counseling, as well as adaptive training skills are also available through community resources.

KEY TERMS

Choriocapillaris—Capillary layer of the choroid.

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Electroretinogram (ERG)—A measurement of electrical activity of the retina.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Retinal pigment epithelium (RPE)—The pigmented cell layer that nourishes the retinal cells; located just outside the retina and attached to the choroid.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

Prognosis

Progression of the disease continues throughout the individual's life, although both the rate and degree of visual loss are variable among those affected, even within the same family.

Resources

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ORGANIZATIONS

American Foundation for the Blind. 11 Penn Plaza, Suite 300, New York, NY 10001. (800) 232-5463.

Choroideremia Research Foundation. 23 E. Brundreth St., Springfield, MA 01109. <http://www.choroideremia.org>.

National Association for Parents of the Visually Impaired. PO Box 317, Watertown, MA 02472. (617) 972-7441 or (800) 562-6265. <http://www.spedex.com/napvi>.

National Eye Institute. 31 Center Dr., Bldg. 31, Room6A32, MSC 2510, Bethesda, MD 20892-2510. <http://www.nei.nih.gov>.

National Federation for the Blind. 1800 Johnson St., Baltimore, MD 21230. (410) 659-9314. epc@roundley.com. <http://www.nfb.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

The Choroideremia Group. <http://www.onelist.com/subscribe.cgi.choroideremia>.

Genevieve T. Slomski, PhD

Chromosomal abnormalities

Chromosomal abnormalities describe changes in the normal number of **chromosomes** or structural problems within the chromosomes themselves. These abnormalities occur when an egg or sperm with an incorrect number of chromosomes, or a structurally faulty chromosome, unites with a normal egg or sperm during conception. Some chromosome abnormalities occur shortly after conception. In this case, the zygote, the cell formed during conception that eventually develops into an embryo, divides incorrectly.

Chromosomal abnormalities can cause serious mental or physical disabilities. **Down syndrome**, for instance, is caused by an extra chromosome 21. People with Down syndrome are mentally retarded and may have a host of physical abnormalities, including heart disorders. Other individuals, called Down syndrome *mosaics*, have a mixture of normal cells and cells with three copies of chromosome 21, resulting in a milder form of the disorder. Most abnormalities in chromosome number lead to the death of the embryo. **Zygotes** that receive a full extra set of chromosomes, a condition called polyploidy, usually do not survive inside the uterus and are spontaneously aborted (a process sometimes called a miscarriage).

Normal number and structure of human chromosomes

A chromosome consists of the body's genetic material, the deoxyribonucleic acid, or **DNA**, along with many kinds of proteins. Within the chromosomes, the DNA is tightly coiled around these proteins (called histones) allowing approximately 6 ft (2 m) strands of DNA to occupy a microscopic space within the nucleus of the cell. When a cell is not dividing, the chromosomes are invisible within the cell's nucleus. Just prior to cell division, the chromosomes begin to replicate and condense. As the replicated DNA condenses, each chromosome looks somewhat like a fuzzy "X" under the microscope. Chromosomes contain the genes, or segments of DNA that code for proteins, of an individual. When a chromosome is structurally faulty, or if a cell contains an abnormal number of chromosomes, the types and amounts of the proteins encoded by the genes is changed. When proteins are altered in the human body, the result can be serious mental and physical changes and disease.

Humans have 46 chromosomes—22 pairs of autosomal chromosomes and one pair of sex chromosomes. These chromosomes may be examined by constructing a **karyotype**, or organized depiction, of the chromosomes. To construct a karyotype, a technician stops cell division just after the chromosomes have replicated and condensed using a chemical, such as colchicine. The chromosomes are visible within the nucleus at this point. The image of the chromosomes seen through the microscope is photographed. Each chromosome is cut out of the picture, and arranged on another sheet in the correct sequence and orientation. The chromosome pairs are identified according to size, shape, and characteristic stripe patterns (called banding).

Normal cell division

In most animals, two types of cell division take place: mitosis and meiosis. In mitosis, each cell division produces two cells that are identical to the parent cell, i.e. one parent cell produces two daughter cells. Compared to its parent chromosome, each daughter cell has exactly the same number of chromosomes and identical genes. This preservation of chromosome number and structure is accomplished through the replication of the entire set of chromosomes just before mitosis.

Sex cells, such as eggs and sperm, undergo a different type of cell division called meiosis. Because sex cells

each contribute half of a zygote's genetic material, sex cells must carry only half the full number of chromosomes. This reduction in the number of chromosomes within sex cells is accomplished during two rounds of cell division, called meiosis I and meiosis II. Before meiosis I, the chromosomes replicate. During meiosis I, a cell with 46 replicated chromosomes divides to form two cells that each contain 23 replicated chromosomes. Normally, the meiosis I division separates the 23 pairs of chromosomes evenly, so that each daughter cell contains one chromosome from each chromosome pair. No replication occurs between meiosis I and meiosis II. During meiosis II, the two daughter cells containing 23 replicated chromosomes divide to form four daughter cells, each containing 23 non-replicated chromosomes. Mistakes can occur during either meiosis I or meiosis II. Chromosome pairs may fail to separate during meiosis I, or a replicated chromosome may fail to separate during meiosis II.

Meiosis produces four daughter cells, each with half the normal number of chromosomes. These sex cells are called haploid cells (haploid means "half the number"). Non-sex cells in humans are called diploid (meaning "double the number") since they contain the full number of normal chromosomes. Human diploid cells normally each have 46 chromosomes, and haploid cells normally each have 23 chromosomes.

Alterations in chromosome number

Two kinds of chromosome number alterations can occur in humans: aneuploidy, an abnormal number of chromosomes, and polyploidy, more than two complete sets of chromosomes.

Aneuploidy

Most alterations in chromosome number occur during meiosis. During normal meiosis, chromosomes are distributed evenly among the four daughter cells. Sometimes, however, an uneven number of chromosomes are distributed to the daughter cells. As noted in the previous section, chromosome pairs may not move apart in meiosis I, or the chromosomes may not separate in meiosis II. The result of both kinds of mistakes (called nondisjunction of the chromosomes) is that one daughter cell receives an extra chromosome, and another daughter cell does not receive any chromosome.

When an egg or sperm that has undergone faulty meiosis and has an abnormal number of chromosomes unites with a normal egg or sperm during conception, the zygote formed will have an abnormal number of chromosomes. This condition is called aneuploidy. There are several types of aneuploidy. If the zygote has an extra chromosome, the condition is called trisomy. If the zygote is missing a chromosome, the condition is called monosomy.

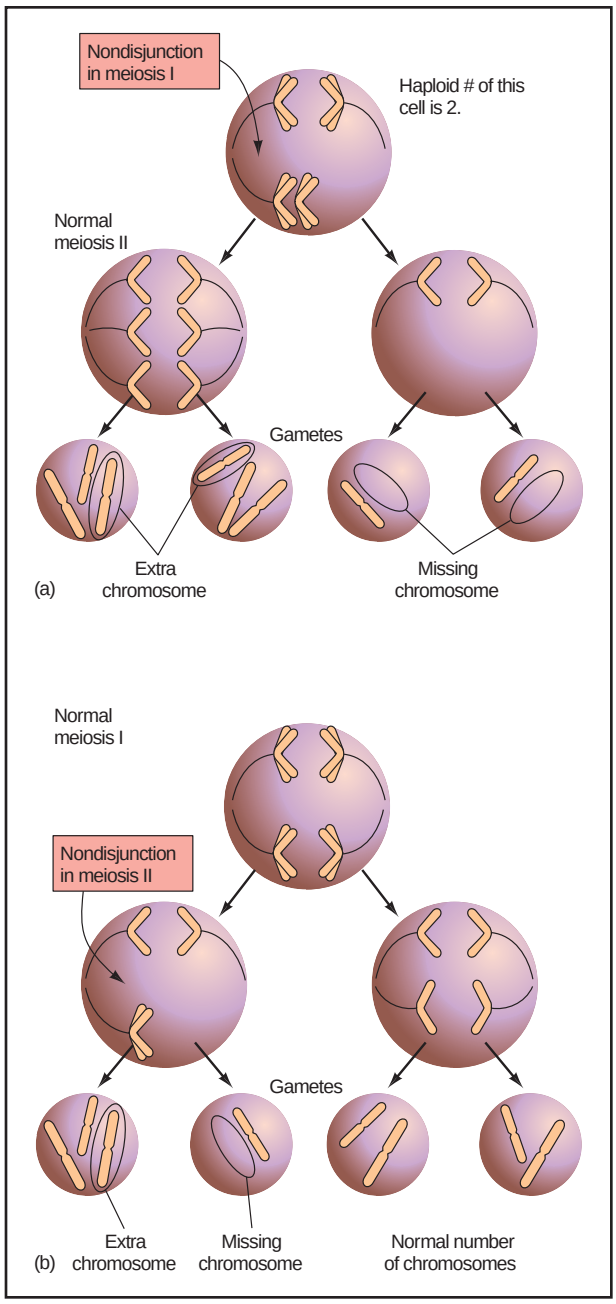

Figure 1. *(Gale Group)*

If the zygote survives and develops into a fetus, the chromosomal abnormality is transmitted to all of its cells. The child that is born will have symptoms related to the presence of an extra chromosome or absence of a chromosome.

Examples of aneuploidy include trisomy 21, also known as Down syndrome, and trisomy 13, also called

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Aneuploidy—An abnormal number of chromosomes in a cell. Trisomy 18 and trisomy 13 are examples of aneuploid conditions.

Angelman syndrome—A syndrome caused by a deletion in the maternally inherited chromosome 15 or uniparental disomy of the paternal chromsome 15.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cri du chat syndrome—A syndrome caused by a deletion in chromosome 5; characterized by a strange cry that sounds like the mewing of a cat.

Deletion—The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Diploid—Means "double number." The normal number of chromosomes (two) for all cells of the human body, except for the sex cells.

Down syndrome—A genetic condition characterized by moderate to severe mental retardation, a characteristic facial appearance, and, in some individuals, abnormalities of some internal organs. Down syndrome is always caused by an extra copy of chromosome 21, or three rather than the normal two. For this reason, Down syndrome is also known as *trisomy 21*.

Duplication—A chromosomal abnormality in which a broken segment of a chromosome attaches to the chromosome pair resulting in extra chromosomal material.

Edwards syndrome—A syndrome caused by trisomy 18; characterized by multi-system disorders; and usually lethal by age 1.

(continued)

Patau syndrome. Trisomy 13 occurs in one out of every 5,000 births, and its symptoms are more severe than those of Down syndrome. Children with trisomy 13 often have cleft palate and eye defects, and always have severe physical and brain malformations. **Trisomy 18**, known as Edwards syndrome, results in severe mutliple defects. Children with trisomy 13 and trisomy 18 usually survive less than a year after birth (Figure 1).

Aneuploidy of sex chromosomes

Sometimes, nondisjunction occurs in the sex chromosomes. Humans have one set of sex chromosomes. These sex chromosomes are called "X" and "Y" after their approximate shapes in a karyotype. Males have both an X and a Y chromosome, while females have two X chromosomes. Disorders associated with abnormal numbers of sex chromosomes are less severe than those associated with abnormal numbers of autosomes. This is thought to be because the Y chromosome carries few genes, and extra X chromosomes are inactivated shortly after conception. Nevertheless, aneuploidy in sex chromosomes causes changes in physical appearance and in fertility (Figure 2).

Individuals with **Klinefelter syndrome**, for instance, are men with two X chromosomes (XXY). This condition occurs in one out of every 600 male births. Men with Klinefelter syndrome have small testes and are usually sterile. Some men with Klinefelter develop enlarged breasts. Males who are XXY are of normal intelligence. However, mental retardation is not unusual in males with more than two X chromosomes, such as XXXY, XXXXY, or XXXXXY.

Males with an extra Y chromosome (XYY) have no physical defects, although they may be taller than aver-

KEY TERMS (CONTINUED)

Fragile X syndrome—A condition caused by an abormality of a region on the X chromosome which may be expressed in males or females, and may increase in severity when inherited from the mother.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Haploid—Means "half the number;" the number of chromosomes in a sex cell.

Inversion—A type of chromosomal defect in which a broken segment of a chromosome attaches to the same chromosome, but in reverse position.

Klinefelter syndrome—A syndrome that occurs in XXY males; characterized by sterility and small testes; normal intelligence.

Meiosis—The process in which a cell in the testes or ovaries undergoes chromosome separation and cell division to produce sperms or eggs.

Metafemale—An out of date term for XXX females, also called triple X syndrome.

Mitosis—The process by which a somatic cell—a cell not destined to become a sperm or egg—duplicates its chromosomes and divides to produce two new cells.

Monosomy—Missing an entire copy of a chromosome or a piece of one copy of a chromosome.

Nucleus—The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

Patau syndrome—A syndrome caused by trisomy 13; characterized by cleft palate, severe mental retardation, and many other physical defects; usually lethal by age 1.

Polyploidy—A condition in which a cell receives more than two complete sets of chromosomes.

Prader-Willi syndrome—A syndrome caused by a deletion in the paternally inherited chromosome 15 or by uniparental disomy of the maternal chromosome 15.

Tetraploidy—A form of polyploidy; four sets of chromosomes.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Triploidy—A form of polyploidy; three sets of chromosomes.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

Turner syndrome—Chromosome abnormality characterized by short stature and ovarian failure, caused by an absent X chromosome. Occurs only in females.

Zygote—The cell formed by the uniting of egg and sperm.

age. XYY males occur in one out of every 1,000 male births.

Females with an extra X chromosome (XXX) are sometimes said to have "triple X syndrome" and were sometimes called metafemales. This defect occurs in one out of every 1,000 female births. Females with XXX do not usually have mental retardation; pubertal development and fertility are normal.

Females with only one X chromosome (XO) have **Turner syndrome**. Turner syndrome is also called monosomy X and occurs in one out of every 2,000-5,000 female births. The sex organs of females with Turner syndrome do not mature at puberty; therefore these women are usually sterile. They are of short stature and have no mental deficiencies. Heart defects are more common in girls with Turner syndrome.

Polyploidy

Polyploidy is lethal in humans. Normally, humans have two complete sets of chromosomes. Normal human cells, other than sex cells, are thus described as diploid. In polyploidy, a zygote receives more than two complete chromosome sets. Examples of polyploidy include triploidy, in which a zygote has three sets of chromosomes, and tetraploidy, in which a zygote has four sets of chromosomes. Triploidy could result from the fertilization of an abnormal diploid sex cell with a normal sex cell or from the fertilization of one egg by two sperm.

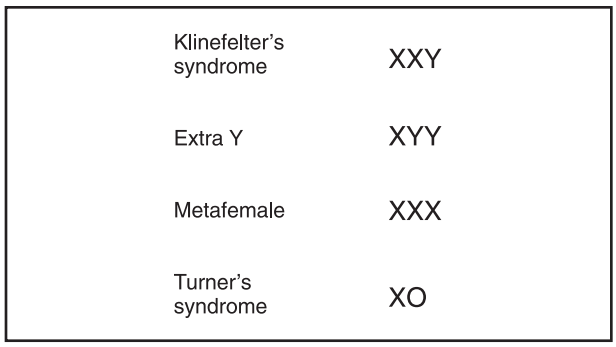

Figure 2. *(Gale Group)*

Tetraploidy could result from the failure of the zygote to divide after it replicates its chromosomes. Human zygotes with either of these conditions usually die before birth, or soon after. Interestingly, polyploidy is common in plants and is essential for the proper development of certain stages of the plant life cycle. Also, some kinds of cancerous cells have been shown to exhibit polyploidy.

Alterations in chromosome structure

Another kind of chromosomal abnormality is changes of chromosome structure. Structural defects arise during replication of the chromosomes just before a meiotic cell division. Meiosis is a complex process that often involves the chromosomes exchanging segments with each other in a process called crossing-over. If the process is faulty, the structure of the chromosomes changes. Sometimes these structural changes are harmless to the zygote; other structural changes, however, can be lethal.

Four types of general structural alterations occur during replication of chromosomes (Figure 3). All four types begin with the breakage of a chromosome during replication. In a deletion, the broken segment of the chromosome is "lost". Thus, all the genes that are present on this segment are also lost. In a duplication, the segment is inserted into the homologous chromosome as extra (duplicated) DNA. In an inversion, the segment attaches to the original chromosome, but in a reverse position. In a translocation, the segment attaches to an entirely different chromosome.

Because chromosomal structural changes cause the loss or misplacement of genes, the results can be quite severe. Deletions and duplications lead to missing and extra chromosomal material, meaning that there are too many or too few genes in that region. Translocations may or may not be harmful. If the translocation is balanced, meaning that all of the DNA is present and none is missing, the only effect may be a higher risk for abnormal sperm or eggs. If the translocation is not balanced, the chance of associated physical and cognitive abnormalities increases. Inversions of DNA may also be harmless except for a risk of abnormal sperm or eggs. However, both inversions and balanced translocations may have clinical consequences, depending on where the breakage and rejoining of DNA occurred.

A structural abnormality in chromosome 21 occurs in about 4% of people with Down syndrome. In this abnormality, a translocation, a piece of chromosome 21 breaks off during meiosis of the egg or sperm cell and attaches to chromosome 13, 14, or 22. The parents of a child with Down syndrome due to this type of translocation could be balanced carriers for the translocation, and if so, are at increased risk to have another child with Down syndrome.

Some structural chromosomal abnormalities have been implicated in certain cancers. For instance, myelogenous leukemia is a **cancer** of the white blood cells. Researchers have found that the cancerous cells contain a translocation of chromosome 22, in which a broken segment switches places with the tip of chromosome 9.

Syndromes associated with chromosomal deletions

Many syndromes are associated with chromosomal deletions. These include **Cri du chat** syndrome, velocardiofacial syndrome, **Prader-Willi syndrome**, **Angelman syndrome**, **Wolf-Hirschhorn syndrome**, **Smith-Magenis syndrome**, **Miller-Dieker syndrome**, **Langer-Giedion syndrome**, and the trichorhinophalangeal syndromes.

Cri du chat means "cat cry" in French. Children with this syndrome have an abnormally developed larynx that makes their cry sound like the meowing of a cat in distress. They also have a small head, misshapen ears, and a rounded face, as well as other systemic abnormalities and mental retardation. Cri du chat is caused by a deletion of a segment of DNA in chromosome 5.

Velocardiofacial syndrome is also called DiGeorge syndrome or Shprintzen syndrome. More recently, it has been called **deletion 22q11 syndrome** because it is caused by a deletion of part of chromosome 22. Individuals with velocardiofacial syndrome may have congenital heart disease, cleft palate, learning difficulties, and subtle characteristic facial features.

Two syndromes caused by a chromosome abnormality illustrate an interesting concept: the severity or type of symptoms associated with a chromosomal defect may depend upon whether the child receives the changed gene from the mother or the father. Both Prader-Willi syn-

drome and **Angelman syndrome** are usually caused by a deletion in chromosome 15. Prader-Willi syndrome is characterized by mental retardation, obesity, short stature, and small hands and feet. Angelman syndrome is characterized by jerky movements and neurological symptoms. People with this syndrome also have an inability to control laughter, and may laugh inappropriately at odd moments. If a child inherits the changed chromosome from its father, the result is Prader-Willi syndrome. But if the child inherits the changed chromosome from its mother, the child will have Angelman syndrome.

A person may have Prader-Willi or Angelman syndrome, but not have the chromosomal deletion usually associated with these conditions. This may be due to a chromosomal error called uniparental disomy. Usually, one of each chromosome pair is inherited from each parent, and every section of DNA has two copies—one maternally inherited and the other paternally inherited. Uniparental disomy refers to the mistake of both copies of a section of DNA being inherited from one parent. Two copies of a maternally inherited chromosome 15 (no paternal **gene** present) causes Prader-Willi syndrome, and two copies of a paternally inherited chromosome 15 causes Angelman syndrome.

The sequence of events leading to Prader-Willi and Angelman syndrome is unknown. Researchers have determined that the genes in this region on chromosome 15 may be "turned off," depending on which parent contributed the chromosome. This process of gene inactivation is called imprinting. Some people have Prader-Willi and Angelman syndrome because the mechanism controlling the imprinting malfunctions.

Expansion of chromosomal material

Not only can the sex of the parent from whom a gene is inherited determine whether it is turned "on" or turned "off," but the sex of the parent may also influence whether certain abnormal sections of chromosomes become more abnormal. For example, the sex of the parent contributing the X chromosome may increase or decrease the chance that a child will be affected with **fragile X syndrome**.

Fragile X syndrome occurs in one out of 1,000 male births and one out of 2,000 female births. Males are affected more severely than females and the syndrome may be more pronounced if the child inherits the disorder from his/her mother. Part of this is explained by the fact that fragile X syndrome is caused by an abnormality of the X chromosome. Remember that a male is XY and a female is XX. A male child receives a Y chromosome from the father and an X chromosome from the mother. A female child, however, can receive an X from either the mother or the father. Girls with fragile X syndrome are less severely affected than boys because they have a normal X chromosome that helps to protect them from the abnormal X chromosome. However, it was somewhat perplexing that girls were affected at all.

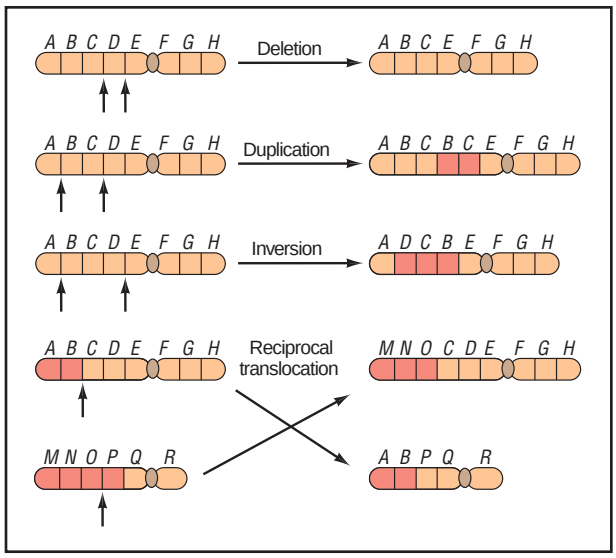

Figure 3. *(Gale Group)*

This mystery was solved when researchers learned that there is a range of abnormality in the fragile X chromosome. If the abnormality of the fragile X region of the chromosome is severe, the influence can be strong enough to affect females. If the abnormality is mild, females will not have symptoms of fragile X syndrome. Furthermore, the fragile X region of the X chromosome may become more severe when it is maternally inherited. The sex of the parent that the region is inherited from affects whether the chromosome abnormality remains stable or becomes greater.

Many other conditions are associated with similar chromosome abnormalities and may remain stable or become more severe depending upon whether the chromosome region is inherited from the mother or the father. In some of these conditions, the region becomes more abnormal when it is paternally inherited. **Huntington disease**, an adult onset neurological disease, is one such condition.

Maternal age and prenatal diagnosis

Currently, no cures exist for any of the syndromes caused by chromosomal abnormalities. For most of the conditions caused by aneuploidy, the risk to give birth to a child with a chromosomal abnormality increases with the mother's age. The risk for Down syndrome, for instance, jumps from one in 1,000 when the mother is age

15-30 to one in 350 at age 35. This is most likely because the risk for nondisjunction as the eggs finish forming increases as maternal age increases. A man's age does not increase the nondisjunction risk because of differences in the way eggs and sperms develop. Sperm are maturing and reproducing throughout a man's adult life. Women, on the other hand, are born with all of the eggs they will ever have. At birth these eggs are part way through meiosis I, and each month as a woman ovulates, one egg finishes meiosis I and begins meiosis II.

People at high risk for chromosomal abnormalities may opt to know whether the fetus they have conceived has one of these abnormalities. **Amniocentesis** is a procedure in which some of the amniotic fluid that surrounds and cushions the fetus in the uterus is sampled with a needle placed in the uterus. Real-time ultrasound is used to guide the procedure. The amniotic fluid contains fetal cells that can be tested for chromosomal, DNA, and biochemical abnormalities. Another test, chorionic villi sampling (CVS), involves taking a piece of tissue from the devloping placenta. Undergoing either amniocentesis or CVS increases the risk of miscarriage slightly. Women and couples considering the procedure should be fully informed of the risks, benefits, and limitations of each procedure. If an abnormality is detected, the prenatal care provider discusses the options available with the woman or couple. Chromosomal abnormalities cannot be corrected. Some parents may terminate the pregnancy. Other parents choose to continue the pregnancy and use the time to prepare for the birth of a child with special needs.

Many resources are available to parents learning of abnormalities before or after birth. In the case of a sex chromosome abnormality, it is common for people to learn of the abnormality as a teenager or even as an adult. A primary care physician, obstetrician, or support group can recommend a specialist from whom more information may be obtained. This specialist is often a medical geneticist, perinatologist, or genetic counselor. Many organizations also provide resources and information to individuals and families.

In conclusion, the division of chromosomes during developmental and during sperm and egg formation is a complex process. Most of the time, however, the process occurs normally. Mistakes that are made can result in changes in chromosome number as well as abnormal chromosomes. Extra or missing chromosomal material usually leads to physical and congnitive defects. Changes in sex chromosome compliment are often associated with milder problems. Some problems with chromosomes are relatively common and are associated with well defined syndromes. Other problems with chromosomes occur rarely and problems associated with the change are only seen in a few individuals.

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American Association for Klinefelter Syndrome Information and Support (AAKSIS) 2945 W. Farwell Ave., Chicago, IL 60645-2925. (773) 761-5298 or (888) 466-5747. Fax: (773) 761-5298. aaksis@aaksis.org <http://www.aaksis.org>.

Angelman Syndrome Foundation. 414 Plaza Dr., Suite 209, Westmont, IL 60559-1265. (630) 734-9267 or (800) 432-6435. Fax: (630) 655-0391. info@angelman.org. <http://www.angelman.org>.

Chromosome Deletion Outreach, Inc. PO Box 724, Boca Raton, FL 33429-0724. (561) 391-5098 or (888) 236-6880. Fax: (561) 395-4252. cdo@worldnet.att.net. <http://members.aol.com/cdousa/cdo.htm>.

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937 info@geneticalliance. <http://www.geneticalliance.org>.

Klinefelter Syndrome and Associates, Inc. PO Box 119, Roseville, CA 95678-0119. (916) 773-2999 or (888) 999-9428. Fax: (916) 773-1449. ksinfo@genetic.org. <http://www.genetic.org/ks>.

National Down Syndrome Congress. 7000 Peachtree-Dunwoody Rd., Bldg 5, Suite 100, Atlanta, GA 30328-1662. (770) 604-9500 or (800) 232-6372. Fax: (770) 604-9898. ndsccenter@aol.com. <http://www.ndsccenter.org>.

National Down Syndrome Society. 666 Broadway, New York, NY 10012-2317. (212) 460-9330 or (800) 221-4602. Fax: (212) 979-2873. <http://www.ndss.org info@ndss.org>.

National Fragile X Foundation. PO Box 190488, San Francisco, CA 94119-0988. (800) 688-8765 or (510) 763-6030. Fax: (510) 763-6223. natlfx@sprintmail.com. <http://nfxf.org>.

Prader-Willi Syndrome Association. 5700 Midnight Pass Rd., Suite 6, Sarasota, FL 34242-3000. (941) 312-0400 or (800) 926-4797. Fax: (941) 312-0142. <http://www.pwsausa.org PWSAUSA@aol.com>.

Triple X syndrome support. 231 W. Park Ave., Sellersville, PA 18960. (215) 453-2117. edr@starbyte.com <http://www.voicenet.com/~markr/triple.html>.

Velo-Cardio-Facial Syndrome Research Institute. Albert Einstein College of Medicine, 3311 Bainbridge Ave., Bronx, NY 10467. (718) 430-2568. Fax: (718) 430-8778. rgoldber@aecom.yu.edu. <http://www.kumc.edu/gec/vcfhome.html>.

WEBSITES

"Angelman Syndrome" *NCI Genes and Disease.* <http://www.ncbi.nlm.nih.gov/disease/angelman.html>.

"Fragile X Syndrome" *NCI Genes and Disease.* <http://www.ncbi.nlm.nih.gov/disease/FMR1.html>.

"Velocardiofacial Syndrome" *NCI Genes and Disease.* <http://www.ncbi.nlm.nih.gov/disease/DGS.html>.

Michelle Bosworth, MS, CGC

Chromosome

Chromosomes are microscopic units containing organized genetic information, located in the nuclei of diploid and haploid cells (e.g. human somatic and sex cells), and are also present in one-cell non-nucleated organisms (unicellular microorganisms), like bacteria, which do not have an organized nucleus. The sum-total of genetic information contained in different chromosomes of a given individual or species are generically referred to as the genome.

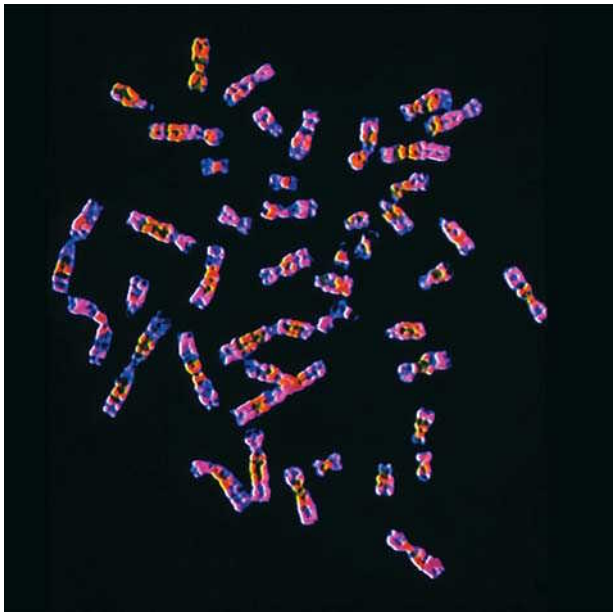
In humans, chromosomes are structurally made of roughly equal amounts of proteins and **DNA**. Each chromosome contains a double-strand DNA molecule, arranged as a double helix, and tightly coiled and neatly packed by a family of proteins called histones. DNA strands are comprised of linked nucleotides. Each nucleotide has a sugar (deoxyribose), a nitrogenous base, plus one to three phosphate groups. Each nucleotide is linked to adjacent nucleotides in the same DNA strand by phosphodiester bonds. Phosphodiester is another sugar, made of sugar-phosphate. Nucleotides of one DNA strand link to their complementary nucleotide on the opposite DNA strand by hydrogen bonds, thus forming a pair of nucleotides, known as a base pair, or nucleotide base. Genes contain up to thousands of sequences of these base pairs. What distinguishes one **gene** from another is the sequence of nucleotides that code for the synthesis of a specific protein or portion of a protein. Some proteins are necessary for the structure of cells and tissues. Others, like enzymes, a class of active (catalyst) proteins, promote essential biochemical reactions, such as digestion, energy generation for cellular activity, or metabolism of toxic compounds. Some genes produce several slightly different versions of a given protein through a process of alternate transcription of base pair segments known as codons.

Amounts of autosomal chromosomes differ in cells of different species; but are usually the same in every cell of a given species. Sex determination cells (mature ovum and sperm) are an exception, where the number of chromosomes is halved. Chromosomes also differ in size. For instance, the smallest human chromosome, the sex chromosome Y, contains 50 million base pairs (bp), whereas the largest one, chromosome 1, contains 250 million base pairs. All three billion base pairs in the human genome are stored in 48 chromosomes. Human genetic information is therefore stored in 24 pairs of chromosomes (totaling 48), 24 inherited from the mother, and 24 from the father. Two of these chromosomes are sex chromosomes (chromosomes X and Y). The remaining 46 are autosomes, meaning that they are not sex chromosomes and are present in all somatic cells (i.e., any other body cell that is not a germinal cell for spermatozoa in males or an ovum in females). Sex chromosomes specify the offspring gender: normal females have two X chromosomes and normal males have one X and one Y chromosome.

Each set of 24 chromosomes constitutes one allele, containing gene copies inherited from one of the parents. The other allele is complementary or homologous, meaning that it contains copies of the same genes and on the same positions, but originated from the other parent. As an example, every normal child inherits one set of copies of gene BRCA1, located on chromosome 13, from the mother and another set of BRCA1 from the father, located on the other allelic chromosome 13. Allele is a Greek-derived word that means "one of a pair," or any one of a series of genes having the same locus (position) on homologous chromosomes.

The first chromosome observations were made under light microscopes, revealing rod-shaped structures in varied sizes and conformations; commonly J-, or V-shaped in eukaryotic cells and ring-shaped chromosome in bacteria. Staining reveals a pattern of light and dark bands. Today those bands are known to correspond to regional variations in the amounts of the two nucleotide base pairs: adenine-thymine (A-T or T-A) in contrast with amounts of guanine-cytosine (G-C or C-G).

Genetic abnormalities and diseases occur when one of the following events happens: a) one chromosome copy is missing, b) extra copies of a chromosome are present, c) a chromosome breaks and its fragment is fused into another chromosome (insertion), d) a fragment is deleted, e) a gene is transferred from one chromosome to another (translocation), f) duplication of a chromosomal segment occurs, g) inversion of a chromosomal seg-



False-colour light micrograph of normal human chromosomes, obtained by amniocentesis. *(Photo Researchers, Inc.)*

ment occurs. **Down syndrome**, for instance, is caused by the presence of a third copy of chromosome 21.

In non-dividing cells, it is not possible to distinguish morphological details of individual chromosomes because they remain elongated and entangled to each other. However, when a cell is dividing, i.e., undergoing mitosis, chromosomes become highly condensed and each individual chromosome occupies a well-defined spatial location.

Mitotic chromosomes present a constricted region, to which the spindle fibers attach during cellular division. Such a constricted region, known as a centromere or primary constriction, may be located in three different positions in chromosomes. Centromeric position allows the classification of chromosomes in three groups: a) acrocentric: centromere lies very near one end; b) metacentric: centromere at the middle, dividing the chromosome in two equal parts or arms; and c) submetacentric: centromere near middle, but dividing chromosome in two unequal arms.

When a chromosome loses its centromere, it is known as acentric. As the centromere is essential for both division and retention of chromosome copies in the new cells, acentric chromosomes will not pass to the daughter cells during the parental cell division. Therefore, daughter cells will miss one chromosome in their **karyotype**. A karyotype map shows mitotic chromosomes in the mitotic phase, known as metaphase. In metaphase, chromosomes align in pairs. In a normal human karyotype, there are 22 pairs of autosomal chromosomes and two sex chromosomes (X and Y). Each pair of autosomal chromosomes contains two complementary or homologous chromosomes, a maternal and a paternal copy.

Some chromosomes also present a secondary constriction that always appears at the same site. They are also useful, along with centromere position and chromosome size, for identifying and characterizing individual chromosomes, in a karyotype.

Karyotype analysis was the first genetic screening utilized by geneticists to assess inherited abnormalities, like additional copies of a chromosome or a missing copy, as well as DNA content and gender of the individual. With the development of new molecular screening techniques and the growing number of identified individual genes, detection of other more subtle chromosomal mutations is now possible (e.g., determinations of gene mutations, levels of gene expression, etc). Such data allow scientists to better understand disease causation and to develop new therapies and medicines for those diseases.

Sandra Galeotti, MS

Chromosome mapping *see* **Gene mapping**

Chronic pancreatitis *see* **Hereditary pancreatitis**

Cleft lip *see* **Cleft lip and palate**

Cleft lip and palate

Definition

A cleft is a birth defect that occurs when the tissues of the lip and or palate of the fetus do not fuse very early in pregnancy. A cleft lip, sometimes referred to as a harelip, is an opening in the upper lip that can extend into the base of the nostril. A cleft palate is an opening in the roof of the mouth.

Description

Infants born with cleft lips will have an opening involving the upper lip. The length of the opening ranges from a small notch to a cleft that extends into the base of the nostril. Cleft lips may involve one or both sides of the lip.

Cleft palates are openings in the palate, which is the roof of the mouth. The size and position of the opening varies. The cleft may only be in the hard palate, the bony portion of the roof of the mouth opening into the floor of the nose, or it may only occur in the soft palate, the soft portion of the roof of the mouth. The cleft palate may involve both the hard and soft palate and may occur on both sides of the center of the palate.

Cleft lips can develop with or without cleft palates. Cleft palates may also occur without cleft lips.

Genetic profile

Cleft lip and palates not associated with a syndrome are caused by a combination of genetic and environmental factors. **Inheritance** caused by such a combination is called multifactorial. The embryo inherits genes that increase the risk for cleft lip and or palate. When an embryo with such genes is exposed to certain environmental factors, the embryo develops a cleft.

The risk of a baby being born with a cleft lip or palate increases with the number of affected relatives and increases with relatives that have more severe clefts.

Environmental factors that increase the risk of cleft lip and palate include cigarette and alcohol use during pregnancy. Some drugs also increase the incidence of clefting, such as phenytoin, sodium valproate, and methotrexate. The pregnant mother's nutrition may affect the incidence of clefting as well.

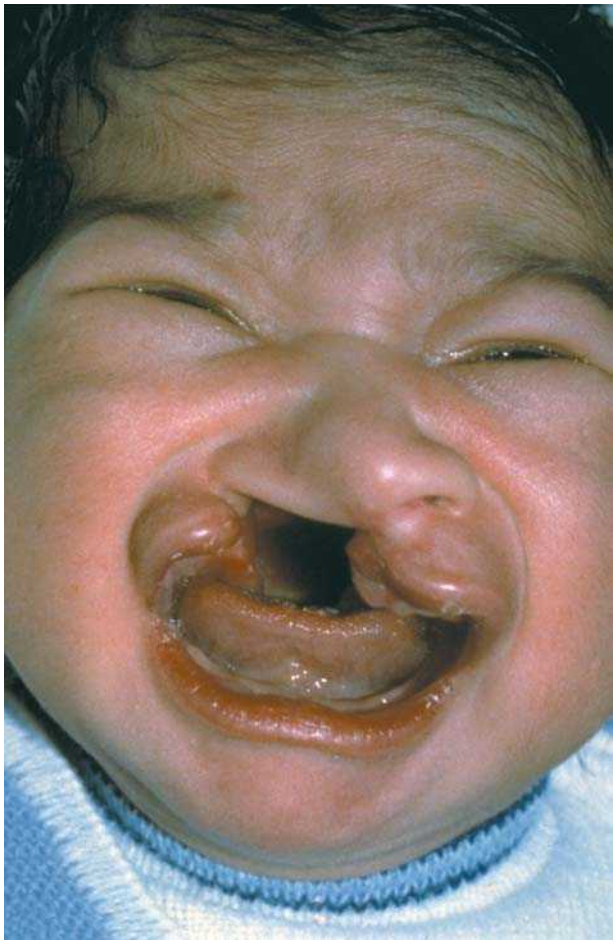
Demographics

The incidence of cleft lip and palate not associated with a syndrome is one in 700 newborns. Native Americans have an incidence of 3.6 in 1,000 newborns. The incidence among Japanese newborns is two in 1,000. The incidence among caucasians is one in 1,000 newborns. African Americans have an incidence of 0.3 in 1,000 newborns.

Signs and symptoms

Babies born with a cleft lip will have an elongated opening in the upper lip. The size of this opening may range from a small notch in the upper lip to an opening that extends into the base of the nostril. The cleft lip may be below the right or left nostril or below both nostrils.

Babies born with a cleft palate will have an opening into the roof of the mouth. The size and position of the cleft varies and it may involve only the hard palate, or only the soft palate and may occur on both sides of the center of the palate.



An infant with a unilateral cleft lip. *(Custom Medical Stock Photo, Inc.)*

In some cases the cleft palate will be covered with the normal lining of the mouth and can only be felt by the examiner.

Infants with cleft lips and palates have feeding difficulties, which are more severe in those with cleft palates. The difficulty in feeding is due to the baby being unable to achieve complete suction. In the case of clefts of the hard palate, liquids enter the nose from the mouth through the opening in the hard palate.

A cleft palate also affects a child's speech, since the palate is necessary for speech formation. The child's speech pattern may still be affected despite surgical repair.

Ear infections are more common in babies born with cleft palates. The infections occur because the muscles of the palate do not open the Eustachian tubes which drain the middle ear. This allows fluid to collect and increases the risk of infection and hearing loss.

Teeth may also erupt misaligned.

Diagnosis

Cleft lip and palate can be diagnosed before birth by ultrasound. After birth, cleft lip and palate are diagnosed by physical exam.

Treatment and management

If cleft lip and/or palate are diagnosed by ultrasound before birth, further testing may be required to diagnose associated abnormalities if present. Referral to a cleft team is essential. A cleft team consists of specialists in the management of patients with clefts and includes surgeons as well as nurses and speech therapists. Members of the team inform the parents of all aspects of management. Feeding methods are also discussed, since feeding is the first problem that must be dealt with. It may be possible to breast feed a baby born with only a cleft lip, but babies born with cleft palates usually have more problems with feeding and frequently require special bottles and teats. A palatal obturator is a device that fits into the roof of the mouth, thus blocking the cleft opening and allowing easier suckling.

Surgery to repair cleft lips is sometimes performed after orthodontic treatment to narrow the gap in the upper lip. The orthodontic treatment can involve acrylic splints with or without screws or may involve the use of adhesive tape placed across the gap in the lip. Orthodontic treatment for cleft lip should begin within the first three weeks of life and continue until the cleft lip is repaired.

The timing of surgical cleft lip repair depends on the judgement of the surgeon who will perform the operation. The procedure is usually performed between one and three months of age. The goals of the operation are to close the gap in the upper lip, place scars in the natural skin curves, and to repair muscle so that the lip appears normal during movement. The closure is done in the three layers (skin, muscle, and mucosa) that line the inside of the lip. At the time of the procedure, if the nose is shaped abnormally due to the cleft lip, it is also corrected. Sometimes further surgery may be needed on the lip and or nose to refine the result.

The goals of the surgeon repairing a cleft palate are normal speech, normal facial growth, and hearing for the affected infant. The repair of the cleft palate is usually performed between three and 18 months of age. The timing may extend beyond this and varies with the type of cleft plate and center where the procedure is being performed. Depending on the type of cleft palate, more than one operation may be needed to close the cleft and improve speech.

Nonsurgical treatment of a cleft palate is available for patients who are at high risk for surgery and consists of a prosthetic appliance worn to block the opening in the palate.

Babies born with cleft palates are vulnerable to ear infections. Their Eustachian tubes do not effectively drain fluid from the middle ear so fluid accumulates and infection sets in. This may lead to hearing loss. These children require drainage tubes to be inserted to prevent fluid accumulation.

Babies born with clefts usually require orthodontic treatment between 13 and 18 years of age. They also require speech therapy.

Prognosis

Individuals with cleft lip and palate have a good prognosis, and approximately 80% will develop normal speech. There is no known means of preventing clefting. Good prenatal care is essential and avoiding harmful substances appear to reduce the risk.

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ORGANIZATIONS

Cleft Palate Foundation. (800) 24-CLEFT. <http://www.cleftline.org>.

Farris F. Gulli, MD

Cleft palate *see* **Cleft lip and palate**

Cleidocranial dysostosis *see* **Cleidocranial dysplasia**

Cleidocranial dysplasia

Definition

Cleidocranial dysplasia (CCD), also known as cleidocranial dysostosis, is a hereditary condition characterized by abnormal clavicles, delayed fusion of the bones in the skull, extra teeth, short stature, and other skeletal changes.

Description

Cleidocranial dysplasia is one of the skeletal dysplasia conditions, a large family of disorders involving abnormal growth and development of the skeleton.

CCD involves a characteristic group of abnormalities affecting primarily the skull, teeth, and clavicles. Other bones, such as the ribs, pelvis, and bones of the hands and feet may also be affected. Older children and adults with CCD are typically shorter than average. Most individuals with this condition do not have significant physical or mental disability.

Genetic profile

CCD is an autosomal dominant condition with variable expressivity (variable symptoms) and complete penetrance (meaning that all individuals who carry the **gene** for CCD have some symptoms). It is estimated that one third of cases represent new mutations, or genetic changes. The gene responsible for CCD has been mapped to the short arm of chromosome 6 and is called CBFA1. This gene encodes a transcription factor, meaning a protein that regulates **DNA** transcription, and is specifically expressed in the bone. Mutations in CBFA1 have been identified in many individuals and families with CCD.

Demographics

More than 500 cases of CCD among individuals of various ethnic backgrounds have been described in the medical literature. The incidence of CCD is reported to be highest around Cape Town, South Africa. The number of affected individuals in this area was estimated to exceed 1,000 as of 1996. These individuals descended from an affected Chinese sailor who settled in the area in 1896 and had seven wives. Study of this large family helped localize the gene responsible for the condition.

Signs and symptoms

Individuals with CCD typically show a delay or failure of the fusion of the calvarial sutures, the openings between the bones of the skull in infants. In some cases, the anterior fontanelle (the "soft spot" on an infant's head) or other areas of the skull may remain unfused through life. A typical facial appearance in persons with CCD includes a broad forehead and widely spaced eyes. The overall head size is usually at the upper limit of normal.

Almost all persons with CCD have some degree of hypoplasia, or underdevelopment, of the clavicles (collar bones). In severe cases, both clavicles may be absent. More commonly, there is hypoplasia of the outside end of the clavicles. Depending on the degree of severity of clavicular hypoplasia, the external appearance of the shoulder may be affected. Some persons with CCD appear to have narrow, sloping shoulders, and some have the unusual ability to bring their shoulders together beneath their chin. This defect usually does not result in physical disability for the individual.

Dental abnormalities are very frequent among persons with CCD and are considered characteristic of the disorder. Almost all individuals are slow to lose their deciduous teeth (baby teeth), with a delay in the eruption of the permanent teeth. Some persons with CCD describe "living without teeth" until their permanent teeth started growing. Additionally, there may be a large number of extra teeth present. These extra teeth are so numerous so as to constitute a more or less complete third set of teeth. Additionally, the enamel of the teeth may be abnormal and prone to decay.

Other signs of CCD include a small rib cage with short or abnormal ribs. The vertebra of the spine may be malformed. The pelvis may be underdeveloped, with an increased space between the pubic bones. The growth of the bones in the hands and feet are often abnormal; most

KEY TERMS

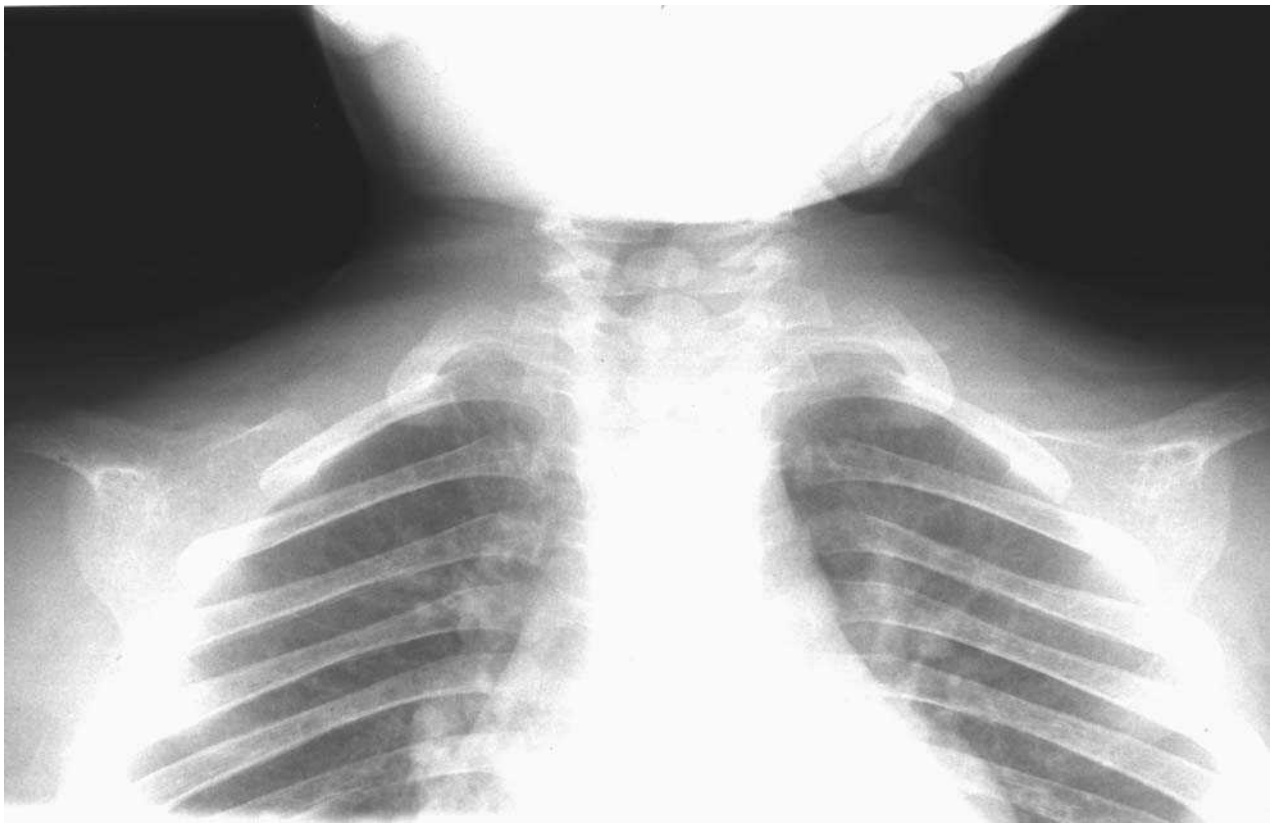
Clavicle—Also called the collarbone. Bone that articulates with the shoulder and the breast bone.

Deciduous teeth—The first set of teeth or "baby teeth".

Fontanelle—One of several "soft spots" on the skull where the developing bones of the skull have yet to fuse.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.



This chest x ray shows the absence of collar bones, a feature common in cleidocranial dysplasia. *(Greenwood Genetic Center)*

are shorter but others are longer than normal. Final height in adults with CCD is usually shorter than expected given the family background.

More unusual complications associated with CCD include **scoliosis** (curvature of the spine), bone fragility, deafness, cleft palate, and a small jaw.

Diagnosis

The diagnosis of CCD is typically made by the doctor following review of the information obtained from physical exams, history, and x ray or other studies. The clavicular hypoplasia may only be seen on x rays.

The combination of hypoplastic clavicles, open fontanelles, and extra teeth is considered typical of CCD. The multiple dental anomalies in CCD are also quite specific and the diagnosis is evident in any individual with normal deciduous teeth, delayed eruption of permanent teeth, and multiple extra teeth.

Testing of the CBFA1 gene for mutations may also be performed. Identification of a mutation may confirm the initial diagnosis, or allow diagnosis before birth.

In a few cases, recognition of the features of CCD by ultrasound imaging, a technique that produces pictures of the fetus, has led to diagnosis of the condition before birth.

Treatment and management

There is no specific treatment for cleidocranial dysplasia. Typically, a course of treatment is designed to manage the specific symptoms.

Children with CCD may be screened for deafness.

Long term dental treatment is often required. Surgery may be performed to remove the baby teeth and open the bony coverings surrounding the permanent teeth, with the goal of promoting their eruption. Orthodontic procedures may be required to align the teeth.

In pregnant females with CCD, the hypoplastic pelvis often necessitates a caesarian section delivery.

Prognosis

CCD is not expected to affect life expectancy in most cases and most diagnosed persons enjoy good overall health.

In some newborns, the small rib cage and reduced lung capacity may lead to respiratory distress. Height is often lower compared to that of other family members. The clavicular hypoplasia does not appear to significantly impair function, and some individuals with hypoplastic or absent clavicles have worked as manual laborers without difficulty. Dental problems are expected, and are sometimes severe enough so as to become a "dental disability". Intelligence is usually normal.

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Jennifer Roggenbuck, MS, CGC

Clubfoot

Definition

Clubfoot is a condition in which one or both feet are twisted into an abnormal position at birth. The condition is also known as talipes.

Description

True clubfoot is characterized by abnormal bone formation in the foot. There are four variations of clubfoot, including talipes varus, talipes valgus, talipes equines, and talipes calcaneus. In talipes varus, the most common form of clubfoot, the foot generally turns inward so that the leg and foot look somewhat like the letter J. In talipes valgus, the foot rotates outward like the letter L. In talipes equinus, the foot points downward, similar to that of a toe dancer. In talipes calcaneus, the foot points upward, with the heel pointing down.

Clubfoot can affect one foot or both. Sometimes an infant's feet appear abnormal at birth because of the intrauterine position of the fetus birth. If there is no anatomic abnormality of the bone, this is not true clubfoot, and the problem can usually be corrected by applying special braces or casts to straighten the foot.

KEY TERMS

Enterovirus—Any of a group of viruses that primarily affect the gastrointestinal tract.

Intrauterine—Situated or occuring in the uterus.

Orthopedist—A doctor specializing in treatment of the skeletal system and its associated muscles and joints.

Genetic profile

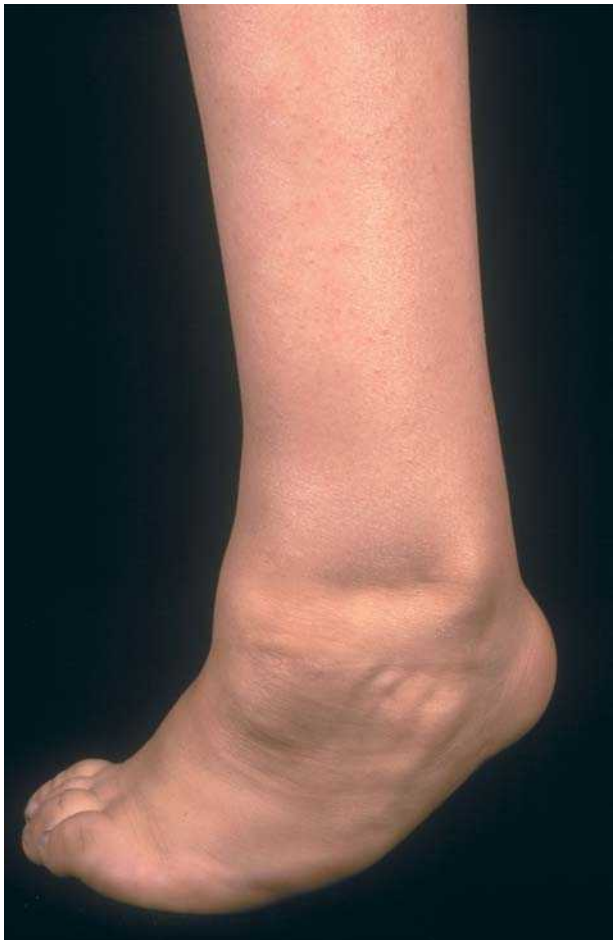
Experts do not agree on the precise cause of clubfoot. The exact genetic mechanism of **inheritance** has been extensively investigated using family studies and other epidemiological methods. As of 1999, no definitive conclusions had been reached, although a Mendelian pattern of inheritance is suspected. This may be due to the interaction of several different inheritance patterns, different patterns of development appearing as the same condition, or a complex interaction between genetic and environmental factors. The MSX1 **gene** has been associated with clubfoot in animal studies. But, as of 2001, these findings have not been replicated in humans.

A family history of clubfoot has been reported in 24.4% of families in a single study. These findings suggest the potential role of one or more genes being responsible for clubfoot.

Several environmental causes have been proposed for clubfoot. Obstetricians feel that intrauterine crowding causes clubfoot. This theory is supported by a significantly higher incidence of clubfoot among twins compared to singleton births. Intrauterine exposure to the drug, misoprostol, has been linked with clubfoot. Misoprostol is commonly used when trying, usually unsuccessfully, to induce abortion in Brazil and in other countries in South and Central America. Researchers in Norway have reported that males who are in the printing trades have significantly more offspring with clubfoot than men in other occupations. For unknown reasons, **amniocentesis**, a prenatal test, has also been associated with clubfoot. The infants of mothers who smoke during pregnancy have a greater chance of being born with clubfoot than are offspring of women who do not smoke.

Demographics

The ratio of males to females with clubfoot is 2.5 to 1. The incidence of clubfoot varies only slightly. In the United States, the incidence is approximately one in every 1,000 live births. A 1980 Danish study reported an overall incidence of 1.20 in every 1,000 children; by



A clubbed foot. *(Photo Researchers, Inc.)*

1994, that number had doubled to 2.41 in every 1,000 live births. No reason was offered for the increase.

Signs and symptoms

True clubfoot is usually obvious at birth. The four most common varieties have been described. A clubfoot has a typical appearance of pointing downward and being twisted inwards. Since the condition starts in the first trimester of pregnancy, the abnormality is quite well established at birth, and the foot is often very rigid. Uncorrected clubfoot in an adult causes only part of the foot, usually the outer edge, or the heel or the toes, to touch the ground. For a person with clubfoot, walking becomes difficult or impossible.

Diagnosis

True clubfoot is usually recognizable and obvious on physical examination. A routine x ray of the foot that shows the bones to be malformed or misaligned supplies a confirmed diagnosis of clubfoot. Ultrasonography is not always useful in diagnosing the presence of clubfoot prior to the birth of a child.

Treatment and management

Most orthopedic surgeons agree that the initial treatment of congenital (present at birth) clubfoot should be non-operative. Non-surgical treatment should begin in the first days of life to take advantage of the favorable fibro-elastic properties of the foot's connective tissues, those forming the ligaments, joint capsules, and tendons. In a common treatment, a series of casts is applied over a period of months to reposition the foot into a normal alignment. In mild cases, splinting and wearing braces at night may correct the abnormality.

When clubfoot is severe enough to require surgery, the condition is usually not completely correctable, although significant improvement is possible. In the most severe cases, surgery may be required, especially when the Achilles tendon, which joins the muscles in the calf to the bone of the heel, needs to be lengthened. Because an early operation induces fibrosis, a scarring and stiffness of the tissue, surgery should be delayed until an affected child is at least three months old.

Much of a clubfoot abnormality can be corrected by the use of manipulation and casting during the first three months of life. Proper manipulative techniques must be followed by applications of appropriately molded plaster casts to provide effective and safe correction of most varieties of clubfoot. Long-term care by an orthopedist is required after initial treatment to ensure that the correction of the abnormality is maintained. Exercises, corrective shoes, or nighttime splints may be needed until the child stops growing.

Prognosis

With prompt, expert treatment, clubfoot is usually correctable. Most individuals are able to wear regular shoes and lead active lives. If clubfoot is not appropriately treated, the abnormality becomes fixed. This has an effect on the growth of the leg and foot, and some degree of permanent disability usually results.

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ORGANIZATIONS

March of Dimes/Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Easter Seal Society. 230 W. Monroe St., Suite 1800, Chicago, IL 60606-4802. (312) 726-6200 or (800) 221-6827. <http://www.easter-seals.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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L. Fleming Fallon, Jr., MD, DrPH

Cobblestone dysplasia *see* **Lissencephaly syndrome**

Cockayne syndrome

Definition

Cockayne syndrome (CS) is a rare inherited disorder that results in an extreme sensitivity to ultraviolet (UV) irradiation, mental retardation, and precocious (premature) aging.

Description

Since first reported in 1936 by Dr. Edward A. Cockayne, less than 200 cases of this disorder have been documented in medical literature. At birth, newborns with CS may have microcephaly (small-sized head) and low birthweight. During the first year of life they do not feed well and, as a result, they suffer from growth failure and delayed development. Ultimately, the disease usually results in death during the teenage years.

Genetic profile

CS results from mutations in the CSA **gene** (also known as the ERCC8 gene) located on chromosome 5. An affected person has inherited one abnormal or nonworking gene from each parent, a pattern that is consistent with autosomal recessive **inheritance**. When functioning normally, the CSA gene helps cells remove and destroy deoxyribonucleic acid (**DNA**) errors from strands undergoing active transcription. Also, the CSA gene allows cells to synthesize ribonucleic acid (**RNA**) after exposure to UV light. Although the parents of an affected child are normal, each of them carries an abnormal gene for CS. Therefore, they have a 25% risk with each pregnancy of having another affected child.

Demographics

CS occurs in less than one in 250,000 births and does not affect any one ethnic group more than another. Males and females are equally affected.

Signs and symptoms

The symptoms of CS are very striking. Failure to grow begins during the first year of life and results in the appearance of dwarfism. The patient's weight is affected more than height. Also, some babies do not feed well and require feeding through a gastrostomy tube (a tube inserted through the abdominal wall into the stomach) to prevent malnutrition. As the infant grows, a delay in developmental milestones becomes apparent around the time that walking and talking should occur. Mental retardation in the mild to moderate range is found in all patients with CS. A small number of patients will have

KEY TERMS

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Fibroblast—Cells that form connective tissue fibers like skin.

Gastrostomy—The construction of an artificial opening from the stomach through the abdominal wall to permit the intake of food.

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Microcephaly—An abnormally small head.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system, which help them conduct impulses more quickly.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Transcription—The process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

severe to profound mental retardation and some never have more than a few words of speech.

Other physical features include sun-sensitive skin, degeneration of retinal pigment, cataracts, and hearing loss. With exposure to sunlight, skin rashes appear and patients develop dry, scaly skin and thin hair. As part of the disease process, the skin develops an aged, leathery appearance. Although the eyes appear normal early in life, the retina later loses its pigment or color and develops a "salt-and-pepper" appearance. If cataracts appear within the first three years of life, the patient usually has the more severe form of CS that leads to death before adolescence. More than half the patients with CS have sensorineural hearing loss. The range of loss is from mild to severe.

Another finding of CS is an unusual gait (walk), caused by a combination of leg spasticity and contractures of the hips, knees, and ankles. The stooped posture often seen in CS results from kyphosis and joint contractures. Some of the first signs of neurologic changes are increased or decreased muscle tone and reflexes.

The most notable sign of CS is precocious senility (premature memory loss and confusion). Patients undergo neurological changes that resemble normal aging; the central and peripheral nervous systems lose myelin and neurons disappear from the central cortex and cerebellum. However, these changes occur at an extremely accelerated pace leading to death during early adolescence.

Diagnosis

Any child who displays these signs should have a genetic examination. CS is diagnosed by excluding other disorders. Specialized testing such as chromosome analysis, chromosome breakage studies, and DNA mutation analysis will rule out other **genetic disorders** such as **Bloom syndrome**, **Werner syndrome**, and **xeroderma pigmentosum**. A person with CS will have a normal complement of 46 **chromosomes**. Their chromosomes also will not show any breakage when subjected to specialized laboratory analysis. DNA testing to look for the specific mutations in the CSA gene is also possible.

Only a very limited number of laboratories can perform the specialized testing that exposes cultured skin fibroblasts to UV irradiation. The fibroblasts of an affected person will lack the ability to form colonies.

Treatment and management

No specific treatment exists for CS. Patients should be treated according to the symptoms they have. Physical therapy will help prevent joint contractures that limit walking. Poor feeders may require a gastrostomy tube to prevent malnutrition. Patients should use sunscreen liberally and limit their exposure to sunlight. Special education will help to maximize the child's learning potential.

Prognosis

The prognosis for CS is grim. Most patients die during the early adolescent years. Some survive until early adulthood. However, some patients have a more severe form and may die during early childhood.

Prevention

Since carriers of the gene that causes CS appear normal, and routine testing before pregnancy is not yet available, couples will not be aware of their risk until they

have an affected child. For future pregnancies, prenatal diagnosis can determine whether or not the baby has CS.

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Suzanne M. Carter, MS, CGC

Coffin-Lowry syndrome

Definition

Coffin-Lowry syndrome (CLS) is an inherited syndrome characterized by mental retardation, slow growth, distinctive facial appearance, large soft hands, loose joints, minor skeletal changes, and low muscle tone (hypotonia). Full expression of the disorder is seen only in males, although females may have some of the physical features and learning disability.

Description

Coffin-Lowry syndrome is one of a large number of mental retardation syndromes caused by abnormalities (mutations) of genes on the X chromosome. The pattern of physical findings, combined with mental retardation, makes the condition readily recognizable and its frequency makes it one of the well-known X-linked mental retardation syndromes. Although CLS was initially considered to be two separate syndromes, Coffin syndrome and Lowry syndrome, the two entities were recognized as the same disease in 1975.

KEY TERMS

Mental retardation—Significant impairment in intellectual function and adaptation in society. Usually associated an intelligence quotient (IQ) below 70.

X-linked—Located on the X chromosome, one of the sex chromosomes. X-linked genes follow a characteristic pattern of inheritance from one generation to the next.

Genetic profile

The **gene** for Coffin-Lowry syndrome, RSK2, is located on the short arm of the X chromosome designated as Xp22. Mutation of the RSK2 gene leads to full expression of the Coffin-Lowry syndrome in males since they only have a single X chromosome. If one of the two RSK2 genes is altered, it leads to some expression of the condition in the form of physical features and learning disabilities. Because females have two X **chromosomes**, CLS is considered inherited as an X-linked semidominant.

Demographics

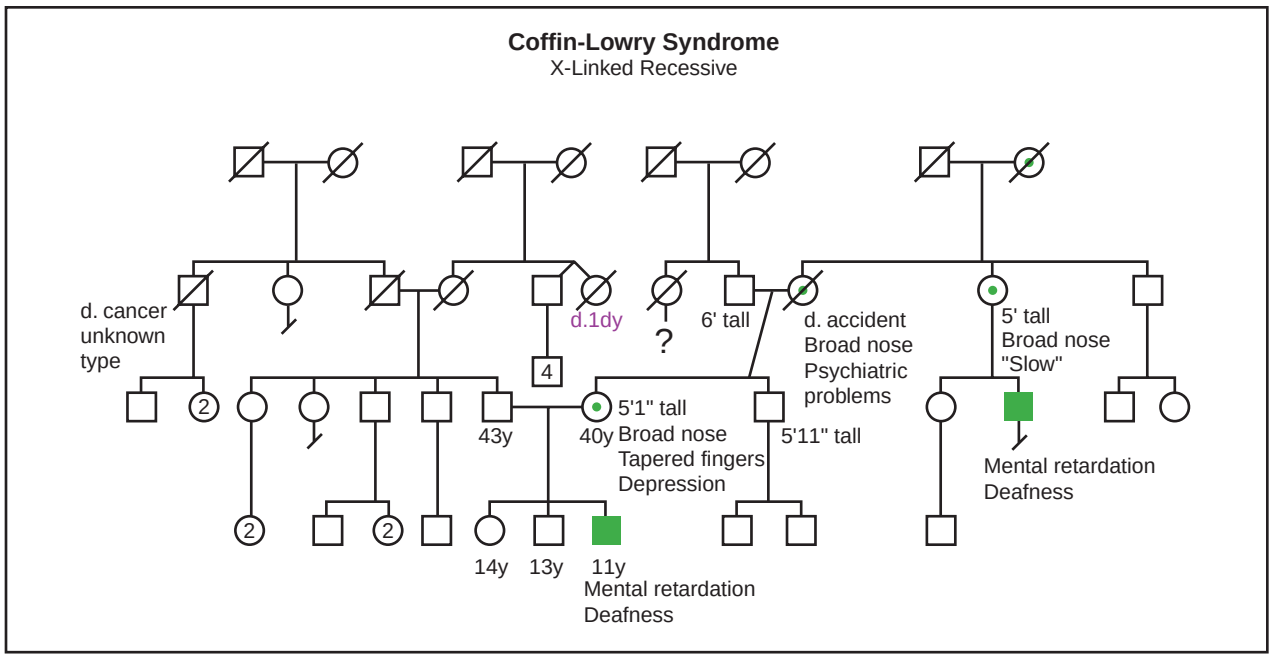
Coffin-Lowry syndrome appears to occur in all populations. The full syndrome is seen in males with lesser expression in carrier females. A prevalence range of one in 50,000-100,000 males has been cited, but no studies with complete case findings have been conducted.

Signs and symptoms

Although the findings in Coffin-Lowry change with age, some manifestations are present from birth. Low muscle tone (hypotonia) and distinctive facial features that include prominent forehead, increased space between the eyes, forward direction of the nostrils, arching of the upper lip, and simple ear structure may be present in infancy. With the passing years, the face elongates, the ears become notably large, the lips and nasal structures thicken, and the mouth is usually open and agape. The hands are large and soft with thick fingers that narrow at their ends. There is generalized looseness at the joints. The central part of the chest may bow outward, the knees are flexed, and the feet flat.

Growth is slow, as manifest by low birth weight, a small head, and short stature during childhood and adult life. All developmental milestones in infancy and childhood are delayed, and intellectual function is severely impaired.

Milder findings consisting of short stature, increased space between the eyes, thick nasal tissues, prominent



(Gale Group)

lips, and soft fleshy hands with thick fingers are consistently seen in carrier females. Intellectual function may be normal or mildly impaired.

Diagnosis

The diagnosis is usually based on the presence of the distinctive facial appearance and mental retardation. In many cases there will be a family history of other affected males or carrier females. X rays may show a number of minor features including delayed maturation of the bones, expansion at the ends of the bones of the digits, notching of the bones of the spine and narrowing of the space between the bones of the spine. The RSK2 gene responsible for Coffin-Lowry syndrome has been isolated, but gene testing is currently available only in research laboratories.

Treatment and management

There is no cure for Coffin-Lowry syndrome. There are no major malformations or specific health problems that pose complications. Because of severe mental retardation, lifelong supervision is generally required. Developmental progress can be promoted by early intervention, speech therapy, and physical therapy.

Prognosis

Long-term survival is the expectation, since individuals with Coffin-Lowry do not have any particular disease susceptibilities, nor do they have any major malformations. However, although there is an overall decrease in longevity in persons with severe mental retardation, specific information on survival in the Coffin-Lowry syndrome is not available.

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Roger E. Stevenson, MD

Coffin-Siris syndrome

Definition

Coffin-Siris syndrome is a rare congenital disorder that affects more females than males. Individuals with this syndrome have some degree of mental retardation or

developmental delay, a coarse facial appearance, incompletely formed or absent fifth fingernails, and absent fifth fingers (distal phalanges). The cause of this disorder is unknown, and the severity of symptoms varies by individual.

Description

Coffin-Siris syndrome was first described in 1970 by Dr. Grange S. Coffin and Dr. Evelyn Siris. It may also be known as fifth digit syndrome. The cause of the disorder is unknown, and the combination of symptoms may vary by individual. All affected children have some form of mental retardation or developmental delay, and incompletely formed (hypoplastic) or absent fifth fingernails and tips of the fifth fingers (distal phalanges). There are some reports of fingers other than the fifth being affected, and affected toes and toenails. The face of a child with Coffin-Siris syndrome is usually described as coarse. This includes a flat nasal bridge, broad nose, wide mouth, thick lips, and in some cases, thick eyebrows, long eyelashes, palate malformations, a large tongue (macroglossia), and a small head (microcephaly). While some infants have an abnormal facial appearance, most of the facial features become more prominent as the child grows. Typically, there is sparse scalp hair in the infant and excessive growth of body hair (hirsutism). Reduced muscle tone (hypotonia), lax joints, delay in bone maturation, and short stature are commonly found. There are reports of frequent upper respiratory and ear infections. Occasionally, children with this disorder have cardiac or spinal abnormalities, hernias, vision or hearing problems, or delayed tooth development (dentition).

Infants with Coffin-Siris syndrome typically have sucking problems and feeding difficulties that may continue as they age. The extent of growth and mental retardation varies by individual. Mental retardation is usually reported as moderate. There are delays in motor activities such as rolling over, sitting up, and walking. Speech is usually delayed. Most children are more capable of responding to speech, rather than verbally expressing themselves.

Genetic profile

At present, the cause of Coffin-Siris syndrome is unknown. Most children reported with this disorder have a normal chromosome set (**karyotype**). There are a few cases in which a transfer of genetic material between **chromosomes** (translocation) has occurred. This may provide information about a specific chromosome site responsible for Coffin-Siris syndrome, but it has not been found in many individuals.

KEY TERMS

Consanguinity—A mating between two people who are related to one another by blood.

Hirsutism—The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Hypotonia—Reduced or diminished muscle tone.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Phalanges—Long bones of the fingers and toes, divided by cartilage around the knuckles.

The majority of cases are sporadic, or random, in which the parents and siblings of an affected child are all healthy. However, there are some cases of affected siblings, and parental relatedness (consanguinity). Coffin-Siris syndrome was originally thought to follow an autosomal recessive pattern of **inheritance**. This would mean that both healthy parents were carriers for the disorder, and the affected child inherited the affected **gene** from both parents. However, there are some reported cases that do not follow this pattern. An exact pattern of inheritance is unknown. The recurrence risk may be as high as 25%.

Demographics

At present, there are reports of more than 60 individuals affected with Coffin-Siris syndrome. It is more common in females, and the female to male ratio may be as high as a 3:1. There are cases of affected siblings, and parental relatedness. In general, cases are random, with affected children having healthy siblings and parents.

Signs and symptoms

At birth, infants with Coffin-Siris syndrome will have an absence or incomplete formation of the fifth fingernail and tip of the fifth finger (distal phalanx). This absence may also occur in the toes or in other fingers. Infants may have an abnormal facial appearance at birth. As the child grows, the facial abnormalities characteristic of Coffin-Siris syndrome become more apparent. Sparse scalp hair in an infant usually becomes more dense with age and excessive hair growth (hirsutism) develops.

Infants typically have sucking problems and feeding difficulties that may continue with age.

There is a delay in both gross and fine motor skills. Developments such as sitting up and walking may be delayed or not possible, depending upon the severity of the disorder. Speech is usually delayed and most children are better able to respond to language rather than express it. Some older children are able to form short sentences and answer simple questions. Mental retardation is usually moderate. Social adaptation is usually delayed.

Diagnosis

At present, the diagnosis of Coffin-Siris syndrome is based upon clinical findings. There are no laboratory tests that can confirm the disorder. The combination of symptoms such as coarse facial appearance, fifth finger appearance, and developmental delay would suggest Coffin-Siris syndrome. X ray of the hands to reveal the absence of the fifth finger bone is usually the best indicator of this syndrome. Neonatal ultrasounds for cardiac, kidney (renal), and other malformations that may be present with this disorder can also be informative.

Prenatal ultrasound may show intrauterine (occurring within the uterus) growth retardation, and can reveal the condition of the fifth finger. However, these symptoms alone cannot conclusively lead to a prenatal diagnosis of Coffin-Siris syndrome.

Due to the rarity, range of symptoms, and variability of Coffin-Siris syndrome, a definitive diagnosis may be difficult. It is important to exclude other disorders that may have similar symptoms. These include **Coffin-Lowry syndrome**, **Cornelia de Lange syndrome**, fetal hydantoin syndrome, trisomy 9p, and Brachymorphism-onychodysplasia-dysphalangism syndrome.

Treatment and management

The treatment or therapy required for children with Coffin-Siris syndrome is based on the particular symptoms of each individual. Some children may require surgery to repair malformations that may be seen with this disorder. This ranges from cleft palate repair to cardiac, renal, or other surgery. Speech therapy and special education may be considered depending upon the degree of mental retardation, developmental delay, and motor impairment.

Prognosis

Infants born with Coffin-Siris syndrome may experience a delay or absence of motor and mental activities, but with support can live into adulthood. The lifestyle of an individual with Coffin-Siris syndrome is dependent to a large extent upon the degree of mental retardation and developmental delay.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

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Maureen Teresa Mahon, BSc, MFS

Cohen syndrome

Definition

Cohen syndrome is a very rare genetic disorder characterized by infantile hypotonia (a weakening of the skeletal muscles), childhood obesity, and several malformations.

Description

Cohen syndrome was first described in 1973 by Dr. M. M. Cohen, Jr. in three children with distinct physical and developmental observations. Since then, over 100 cases have been reported throughout the world, offering the picture of an extremely rare disease with a wide range of clinical characteristics. The initial description given by

Cohen included obesity, mental retardation, low muscle tone, narrow hands and feet, and distinctive facial features with prominent upper central teeth. As of 2001, the underlying cause of the disease remains unknown.

Cohen syndrome has also been referred to as Pepper syndrome, Hypotonia-Obesity-Prominent Incisors syndrome, Obesity-Hypotonia syndrome, and Mirhosseini-Holmes-Walton syndrome.

Genetic profile

Research has suggested that the **gene** for Cohen syndrome lies between 8q21.3 and 8q22.1. This refers to a location on the long arm of chromosome 8 between positions 21.3 and 22.1 and is a rough estimate of where the gene may lie. This region was originally referred to as CHS1 but has since become known as COH1. The phrase 'COH1 gene region' is often used due to the fact that the exact location of the gene still remains to be discovered.

Chromosomes are the genetic material passed down from generation to generation that tell a person's body how to work and how to grow. Each chromosome is composed of smaller pieces known as genes. A person inherits one set of 23 chromosomes from both the egg and the sperm of the parents. These chromosomes can then be matched into pairs, giving two copies of each chromosome and likewise two copies of each gene.

Cohen syndrome is an autosomal recessive disorder. Recessive means that both copies of the COH1 gene region must have a change or mutation for a person to be affected. An individual with only one changed COH1 gene region is not affected by the disease but can pass the disease on to a future child. These individuals are called carriers. If two carriers have a child there is a 25% chance with each pregnancy that the child will be affected. At this time prenatal diagnosis is not available.

Demographics

While Cohen syndrome affects all races and genders, several small samplings of affected populations have been studied around the world. Interestingly, it has been found that Cohen syndrome manifests in these populations in distinctly different ways, with certain clinical findings being family- or ethnic-specific.

For example, Cohen syndrome has been studied extensively in Finland. In the populations studied, individuals diagnosed with the syndrome typically have fewer white blood cells than normal (granulocytopenia), a specific eye abnormality called mottled retina, and mental retardation. As a rule, they do not have truncal obesity, a common characteristic of Cohen syndrome in other populations. Although the symptoms of Cohen syndrome are known to vary widely between affected individuals within the same family, affected people within the Finnish populations are very similar to each other in their presentation.

Due to the extreme rarity of the disease, the exact incidence of Cohen syndrome is not known. A relatively high frequency of the disease has also been noted in Israel. However, earlier reports suggesting a possible increase in the frequency of Cohen syndrome among Ashkenazi Jews no longer seems to be true.

KEY TERMS

Astigmatism—A cause of poor eyesight, usually due to an error in the refraction of light within the eye.

Autism—A syndrome characterized by a lack of responsiveness to other people or outside stimulus, often in conjunction with a severe impairment of verbal and non-verbal communication skills.

Autosome—Chromosome not involved in specifying sex.

Coloboma of the iris—A birth defect leading to missing structures within the eye.

Granulocytopenia—A reduced number of white blood cells in the circulation.

Hypotonia—Reduced or diminished muscle tone.

Leucopenia—A decrease in white blood cells.

Microphthalmia—Small or underdeveloped eyes.

Mottled retina—Changes in the retina of the eye causing a loss of visual acuity.

Myopia—Nearsightedness. Difficulty seeing objects that are far away.

Neutropenia—A condition in which the number of leukocytes (a type of white or colorless blood cell) is abnormally low, mainly in neutrophils (a type of blood cell).

Philtrum—The center part of the face between the nose and lips that is usually depressed.

Retinal dystrophy—Degeneration of the retina, causing a decline in visual clarity.

Signs and symptoms

Four main areas are affected by Cohen syndrome: physical appearance, mental function, vision, and hema-

tology (blood function). The list of possible conditions is extensive however, and it is important to remember that each case is different. While a given characteristic may be common to the syndrome, not all affected individuals have been found to have it.

Physical appearance

When they are born, babies with Cohen syndrome usually look just like babies without the syndrome, although they are typically born at a low birth weight. As they grow, the various physical signs associated with the syndrome become increasingly obvious.

Narrow hands and feet with long slender fingers are a hallmark feature, found in approximately 89% of diagnosed individuals. Truncal obesity, or the abnormal deposition of fat around the mid-section of the body, has been observed in roughly 70% of patients. Most individuals with Cohen syndrome have large and rather noticeable front teeth, referred to as prominent upper central incisors. In general, the teeth are abnormal in shape and position. A majority of individuals with Cohen syndrome are also short, with many experiencing growth deficiency at all stages of life. Microcephaly (small head) is another common feature of the syndrome.

In addition, there are many other associated physical characteristics that occur less often. The palate (roof of the mouth) may be overly high, arched, and narrow. The mid-face can have an underdeveloped appearance and the area below the nose to the upper lip (philtrum) may be very short. The eyes can be down-slanting and thick hair and eyebrows may be observed.

Mental dysfunction

It is thought that every individual with Cohen syndrome experiences some level of developmental delay. Mental retardation can range from mild to severe. Even from infancy many are obviously behind in developmental milestones and are not able to sit up or roll over within the same time frame as their peers.

Most children with Cohen syndrome do learn to walk, although there have been a few reported cases of individuals who were wheelchair-bound. There is usually a noticeable delay, with affected children not learning to walk independently until much later than their peers (the normal average age for walking independently is 12 months).

Language deficiencies are also a common occurrence. Many affected individuals never learn to talk or have a vocabulary limited to a few singular words and two-word phrases. In general an IQ of less than 50 is considered average for Cohen syndrome.

Visual deficiencies

Vision is affected to varying degrees. Severe limitation in eyesight due to **myopia** is often observed. Several other dysfunctions and defects of the eyes causing low visual clarity have been reported including retinal dystrophy, strabismus, astigmatism, microphthalmia, and **coloboma** of the iris.

Hematologic abnormalities

Cohen syndrome can have a profound effect on the composition of the blood. Abnormally low counts of white blood cells, referred to as granulocytopenia, was once thought to be a standard symptom. It was hoped that it could help in early diagnosis because it can be tested for at birth. However, further studies have shown that not all affected individuals suffer from granulocytopenia. Some individuals have no blood disorders associated with their disease at all while others have various forms of white blood cell problems, such as a reduction in the number of white blood cells in the blood (leucopenia) or of neutrophils, which are specialized white blood cells (neutropenia).

Other deficiencies

Hypotonia, or low muscle tone, is found in 90-100% of the persons diagnosed with Cohen syndrome. Babies with hypotonia are described as “floppy” due to their lack of muscle strength. Although the observed hypotonia is not thought to be associated with any nervous system disorder, it does delay the overall development of the child, most notably in slowing the development of motor skills.

Social skills

Many studies have described Cohen syndrome patients as being outgoing and friendly with mild hyperactivity and severe attention deficits. There are a few reports of diagnosed individuals showing signs of **autism**, an extreme form of centering attention and interest on the self only.

Diagnosis

In 1972, Dr. Mirhosseini and others described two patients with symptoms similar to those observed in Cohen syndrome. These patients and a few subsequent cases were given a diagnosis of Mirhosseini-Holmes-Walton syndrome. Over the years, scientific opinion has come to consider Mirhosseini-Holmes-Walton syndrome and Cohen syndrome as different manifestations of the same disease.

Diagnosis of Cohen syndrome is difficult due to the varied nature of the symptoms. Most features of Cohen

syndrome are not evident in the newborn and many symptoms, such as truncal obesity and visual deficits are not easily observed until early childhood. In the past, the average age of diagnosis was approximately 6-8 years. However, as physicians become more aware of the disorder it is hoped that diagnosis will occur at earlier ages, offering affected individuals the opportunity for rapid intervention and treatment.

Incorrect diagnosis is not uncommon in patients with Cohen syndrome. Affected individuals may be misdiagnosed with **Marfan syndrome**, **Sotos syndrome**, hypothyroidism, **Prader-Willi syndrome**, or mental retardation of an unknown nature.

A correct and early diagnosis is important to ensure the favorable prognosis of the patient and so that the family can receive appropriate **genetic counseling** concerning the affected child or the risks involved in future pregnancies.

Treatment and management

Treatment of Cohen syndrome is focused on improving or alleviating symptoms as they arise. There is no cure for Cohen syndrome.

Early correction of vision problems, usually with glasses, often leads to general improvement of cognitive skills, an area of marked deficit in affected individuals.

As is the case for many disorders involving hypotonia and slowed development, physical and occupational therapy are invaluable tools. These treatment strategies are important at any age, but should be started as early as possible. There is no need to wait for a definitive diagnosis of Cohen syndrome as any child with hypotonia can benefit from physical and occupational therapy.

Prognosis

Varying symptoms lead to varying prognosis. Mental retardation can range from mild to severe. However, there is no way to predict the level of developmental delay a specific child will experience. Language deficiencies also vary a lot, with some children never learning to speak at all and others speaking full sentences. The hypotonia observed in infancy may persist and moderate obesity usually develops in mid-childhood.

As of 2001, there has been one reported case of a woman with Cohen syndrome giving birth. The child had some developmental delays but was thought not to have Cohen syndrome.

Resources

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Young, I.D., and J. Moore. "Intrafamilial variation in Cohen syndrome." *Journal of Medical Genetics* 24 (1987): 488-492.

ORGANIZATIONS

International Cohen Syndrome Support Group. 7 Woods Court, Brackley, Northants, NN13-6HP. UK (012) 80–704515.

WEBSITES

NORD—National Organization for Rare Diseases, Inc. <http://www.rarediseases.org>.

The Arc: A National Organization on Mental Retardation. <http://www.thearc.org>.

Java O. Solis, MS

Coloboma

Definition

Coloboma, also known as keyhole defect of the iris, is a congenital genetic disorder that affects the iris of the eye. Present at birth, coloboma implies the absence of tissue.

Description

A coloboma describes a condition wherein a portion of a structure of the eye is absent, usually the iris, retina, or the optic nerve. The disorder is often referred to as a keyhole defect of the iris because the shape of the coloboma appears as the shape of a keyhole or an upside-down pear. There are many different types of colobomas, as described below.

Types of colobomas:

- Optic disc coloboma. This disorder occurs when the coloboma covers the optic nerve and may involve the macula, a structure in the eye that is responsible for visual acuity.
- Iris coloboma. This type of coloboma may be in one eye (unilateral) or in both eyes (bilateral). The pupil is often described as an upside-down pear shape when an individual has an iris coloboma.
- Retinal coloboma. In this disorder, a notch or cleft of the retina or part of the retina is missing. For example, 35% or more of the retina may be missing.
- Choroidal coloboma. This condition is similar to a retinal coloboma. The choroid is a structure in the eye that lies between the sclera and the retina.
- Morning glory syndrome. This condition, a type of optic nerve coloboma, affects the shape of the optic nerve. The syndrome is aptly named because it

KEY TERMS

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Macula—A small spot located in the back of the eye that provides central vision and allows people to see colors and fine visual details.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Pupil—The opening in the iris through which light enters the eye.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Sclera—The tough white membrane that forms the outer layer of the eyeball.

describes the appearance of the optic nerve, which looks like the inside of a morning glory flower.

Genetic profile

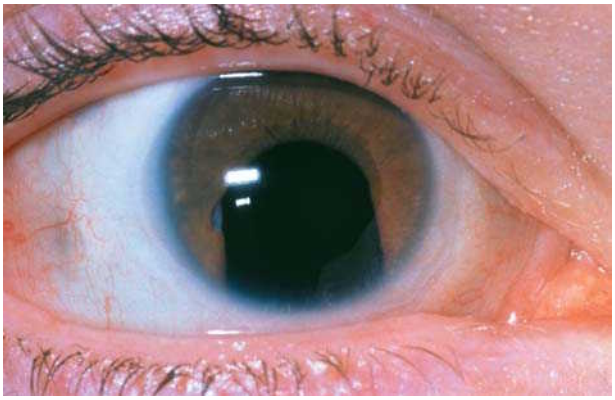
Colobomas may be isolated abnormalities in otherwise normal individuals or they may occur as part of a syndrome. As isolated findings, they are generally sporadic (not inherited). Some families, however, have shown an autosomal dominant **inheritance** pattern, meaning only one copy of the abnormal **gene** needs to be present for the disorder to occur. Some of the **genetic disorders** thought to contribute to coloboma include cat-eye syndrome, trisomy 13, **trisomy 18**, **Sturge-Weber syndrome**, and basal cell nevus syndrome.

Demographics

The condition occurs in about one in 10,000 births. Coloboma may be associated with hereditary or genetic conditions, trauma to the eye, or eye surgery.

Signs and symptoms

Chorioretinal colobomas are those that affect the choriod (light impermeable lining consisting primarily of blood vessels) and the retina (the photosensitive lining inside the eye). The extent to which vision would be impaired depends on the size of the coloboma, and its impact on the optic nerve and macula. A coloboma can appear as a black indentation of varying depth at the edge of the pupil, and gives the pupil an odd or irregular shape. It may also appear as a split in the iris from the pupil to the edge of the iris.



The pupil in this eye is enlarged, extending to the lower edge of the cornea. Colobomas form because of a failure of the rudimentary eye to join the optic fissure during embryonic development. *(Photo Researchers, Inc.)*

Symptoms usually present as blurred or decreased vision, and an appearance of a hole or odd-shaped pupil in the individual's eye. A smaller colboma, especially if it is not attached to the pupil, often causes a secondary image to focus on the back of the eye, producing blurred vision or decreased visual sharpness.

Diagnosis

A diagnosis is made by a physical exam and includes a detailed eye examination by an opthalmologist. The ophthalmologist will also ask the individual when the symptoms were first noticed, determine what part of the eye is affected, the size and shape of the dark area in the eye, and ask for reports of any changes in the individual's vision.

Certain diagnostic tests are often used to diagnose coloboma. These include a visual acuity test, refraction test, and an in-depth history of symptoms.

Treatment and management

Colobomas may be accompanied by other problems that may be neurological or chromosomal in nature. In addition, some genetic syndromes also include coloboma as part of the disorder's potential findings. More importantly, a specific combination of abnormalities identified by the acronym CHARGE must also be considered when a diagnosis of coloboma is made.

The medical condition known as **CHARGE association** is a very rare and serious condition. Individuals that have the condition will require attention from several specialists and treatment from an early age. Colobomas are usually one of the findings in individuals with CHARGE. The disorder includes these problems:

- (C)oloboma
- (H)eart defects
- (A)tresia of the choanae, which is a blockage of the nasal passages
- (R)etarded growth and development
- (G)enital hypoplasia, which occurs when the testes do not descend properly
- (E)ar abnormalities

While there is no specific treatment for coloboma, some treatments are available that can manage vision problems associated with the disorder. For example, physicians often recommend cosmetic contact lenses and sunglasses for individuals whose eyesight is adversely affected. Additional optical aids are often helpful such as eye patching. Since many indivduals with coloboma are highly sensitive to light, opthalmologists often recommend special lights or other personalized visual aids.

Prognosis

The effects of coloboma can be mild or severe, depending upon the extent and location of the gap or cleft. The gap itself is usually located at the bottom of the eye, but it may occur in the iris, choroid, macula or optic nerve.

A coloboma of the lens, particularly if it is large, may also include abnormalities of the iris and choroids, which increases the risk of retinal tearing. In severe cases of coloboma, the eye may be reduced in size. This condition is called microphthalmous, a disorder that can arise with or without coloboma.

The specific gene or genes responsible for coloboma have not yet been identified, but research continues throughout the United States, Scotland, and England.

Resources

ORGANIZATIONS

Royal National Institute for the Blind. PO Box 173, Peterborough PE2 6WS. <http://www.rnib.org.uk>.

WEBSITES

Coloboma. <http://www.coloboma.org/whatis.html>.

Medlineplus. <http://www.medline.adam.com/ency/article/003318.htm>.

Bethanne Black

Coloboma-obesity-hypogenialism-mental retardation syndrome *see* Coloboma

Color blindness

Definition

Color blindness is an abnormal condition characterized by the inability to clearly distinguish different colors of the spectrum. The difficulties can be mild to severe. It is a misleading term because people with color blindness are not blind. Rather, they tend to see colors in a limited range of hues; a rare few may not see colors at all.

Description

Normal color vision requires the use of specialized receptor cells called cones, which are located in the retina of the eye. There are three types of cones, termed red, blue, and green, which enable people to see a wide spectrum of colors. An abnormality, or deficiency, of any of the types of cones will result in abnormal color vision.

There are three basic variants of color blindness. Red/green color blindness (deuteranopia) is the most common deficiency, affecting 8% of Caucasian males and 0.5% of Caucasian females. The prevalence varies with culture.

Blue color blindness (protanopia) is an inability to distinguish both blue and yellow, which are seen as white or gray. Protanopia is quite rare and has equal prevalence in males and females. It is common for young children to have blue/green confusion that becomes less pronounced in adulthood. Blue color deficiency often appears in people who have physical disorders such as liver disease or **diabetes mellitus**.

A total inability to distinguish colors (achromatopsia) is exceedingly rare. These affected individuals view the world in shades of gray. They frequently have poor visual acuity and are extremely sensitive to light (photophobia), which causes them to squint in ordinary light.

Genetic profile

Red/green and blue color blindness appear to be located on at least two different **gene** locations. The majority of affected individuals are males. Females are carriers but are not normally affected. This indicates that the X chromosome is one of the locations for color blindness. Male offspring of females who carry the altered gene have a fifty-fifty chance of being color-blind. The rare female that has red/green color blindness, or rarer

KEY TERMS

Achromatopsia—The inability to distinguish any colors.

Cones—Receptor cells that allow the perception of colors.

Deuteranopia—The inability or difficulty in distinguishing red/green colors.

Photophobia—An extreme sensitivity to light.

Protanopia—The inability or difficulty in distinguishing blue and yellow colors.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Rod—Photoreceptor that is highly sensitive to low levels of light and transmits images in shades of gray.

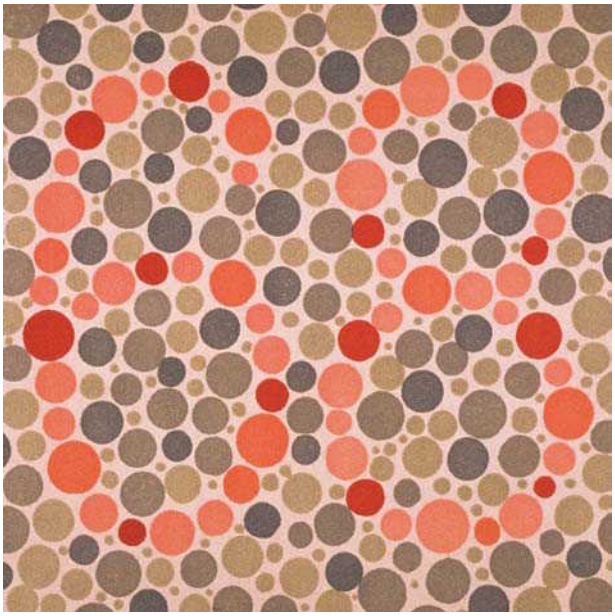
still, blue color blindness, indicates there is an involvement of another gene. As of 2001, the location of this gene has not been identified.

Achromatopsia, the complete inability to distinguish color, is an autosomal recessive disease of the retina. This means that both parents have one copy of the altered gene but do not have the disease. Each of their children has a 25% chance of not having the gene, a 50% chance of having one altered gene (and, like the parents, being unaffected), and a 25% risk of having both the altered gene and the condition. In 1997, the achromatopsia gene was located on chromosome 2.

Demographics

Researchers studying red/green color blindness in the United Kingdom reported an average prevalence of only 4.7% in one group. Only 1% of Eskimo males are color blind. Approximately 3% of boys from Saudi Arabia and 4% from India were found to have deficient color vision. Red/green color blindness may slightly increase an affected person's chances of contracting leprosy. Pre-term infants exhibit an increased prevalence of blue color blindness. Achromatopsia has a prevalence of about one in 33,000 in the United States and affects males and females equally.

Color blindness is sometimes acquired. Chronic illnesses that can lead to color blindness include **Alzheimer disease**, **diabetes mellitus**, **glaucoma**, leukemia, liver disease, chronic **alcoholism**, **macular degeneration**, multiple sclerosis, **Parkinson disease**, **sickle cell anemia**, and **retinitis pigmentosa**. Accidents



A common test used to detect color blindness. The number "hidden" in the image will not be visible to an individual with red/green color blindness. *(Corbis)*

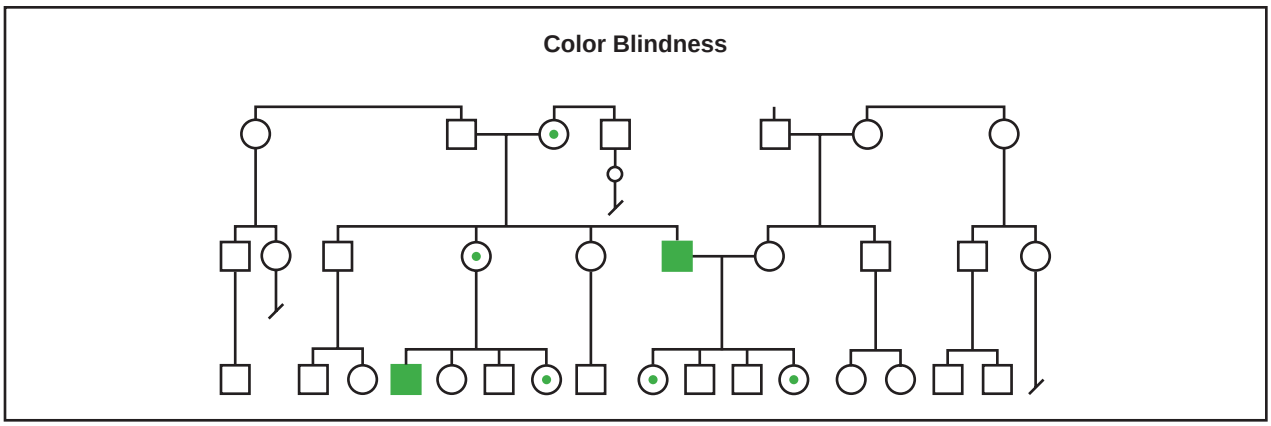
or strokes that damage the retina or affect particular areas of the brain can lead to color blindness. Some medications such as antibiotics, barbiturates, anti-tuberculosis drugs, high blood pressure medications, and several medications used to treat nervous disorders and psychological problems may cause color blindness. Industrial or environmental chemicals such as carbon monoxide, carbon disulfide, fertilizers, styrene, and some containing lead can cause loss of color vision. Occasionally, changes can occur in the affected person's capacity to see colors after age 60.

Signs and symptoms

The inability to correctly identify colors is the only sign of color blindness. It is important to note that people with red/green or blue varieties of color blindness use other cues such as color saturation and object shape or location to distinguish colors. They can often distinguish red or green if they can visually compare the colors. However, most have difficulty accurately identifying colors without any other references. Most people with any impairment in color vision learn colors, as do other young children. These individuals often reach adolescence before their visual deficiency is identified.

Diagnosis

There are several tests available to identify problems associated with color vision. The most commonly used is



(Gale Group)

the American Optical/Hardy, Rand, and Ritter Pseudoisochromatic test. It is composed of several discs filled with colored dots of different sizes and colors. A person with normal color vision looking at a test item sees a number that is clearly located somewhere in the center of a circle of variously colored dots. A color-blind person is not able to distinguish the number.

The Ishihara test is comprised of eight plates that are similar to the American Optical Pseudoisochromatic test plates. The individual being tested looks for numbers among the various colored dots on each test plate. Some plates distinguish between red/green and blue color blindness. Individuals with normal color vision perceive one number. Those with red/green color deficiency see a different number. Those with blue color vision see yet a different number.

A third analytical tool is the Titmus II Vision Tester Color Perception test. The subject looks into a stereoscopic machine. The test stimulus most often used in professional offices contains six different designs or numbers on a black background, framed in a yellow border. Titmus II can test one eye at a time. However, its value is limited because it can only identify red/green deficiencies and is not highly accurate.

Treatment and management

There is no treatment or cure for color blindness. Most color vision deficient persons compensate well for their abnormality and usually rely on color cues and details that are not consciously evident to persons with typical color vision.

Inherited color blindness cannot be prevented. In the case of some types of acquired color deficiency, if the cause of the problem is removed, the condition may improve with time. But for most people with acquired color blindness, the damage is usually permanent.

Prognosis

Color blindness that is inherited is present in both eyes and remains constant over an individual's entire life. Some cases of acquired color vision loss are not severe, may appear in only one eye, and can last for only a short time. Other cases tend to be progressive, becoming worse with time.

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Osuobeni, E. P. "Prevalence of Congenital Red-Green Color Vision Defects in Arab Boys from Riyadh, Saudi Arabia." *Ophthalmic Epidemiology* 3 (3) (December 1996): 167-170.

ORGANIZATIONS

Achromatopsia Network. C/O Frances Futterman, PO Box 214, Berkeley, CA 94701-0214. <http://www.achromat.org/how_to_join.html>.

American Academy of Ophthalmology. PO Box 7424, San Francisco, CA 94120-7424. (415) 561-8500. <http://www.eyenet.org>.

International Colour Vision Society: Forschungsstelle fuer Experimentelle Ophthalmologie. Roentgenweg 11, Tuebingen, D-72076. Germany <http://orlab.optom.unsw.edu.au/ICVS>.

National Society to Prevent Blindness. 500 East Remington Rd., Schaumburg, IL 60173. (708) 843-2020 or (800) 331-2020. <http://www.preventblindness.org>.

WEBSITES

"Breaking the Code of Color." *Seeing, Hearing and Smelling the World*. <http://www.hhmi.org/senses/b/b130.htm>.

"Color Blindness." *Geocities*. <http://www.geocities.com/Heartland/8833/coloreye.html>.

"Medical Encyclopedia: Colorblind." *MEDLINEplus*. <http://medlineplus.adam.com/ency/article/001002sym.htm>.

University of Manchester. <http://www.umist.ac.uk/UMIST_OVS/welcome.html>.

University of Nevada–Reno. <http://www.delamare.unr.edu/cb/>.

L. Fleming Fallon, Jr., MD, DrPH

Cone-rod dystrophy

Definition

Cone-rod dystrophy (CRD) is a progressive retinal degenerative disease that causes deterioration of the cones and rods in the retina and frequently leads to blindness. Cone-rod dystrophy is also accompanied by amelogenesis imperfecta, an abnormality affecting the teeth.

Description

Cone-rod dystrophy is characterized by all of the following elements: skin pigmentation abnormality; involuntary, rhythmic movements of the eyes (nystagmus); degeneration of vision (optic atrophy); and sensitivity to light (photophobia).

Cone-rod dystrophy can be inherited as either an autosomal dominant or autosomal recessive trait. In its most common form, however, it is usually inherited as an autosomal recessive trait, which means that both parents have one copy of the cone-rod dystrophy **gene** but do not have the disease. Autosomal recessive cone-rod dystrophy (arCRD) is a genetically heterogeneous disease with changes (mutations) in the ABCR gene. These mutations cause an abnormality in rod outer segment function that ultimately leads to dysfunction or death of the photoreceptor cells in the retina.

Genetic profile

The CRX gene has been shown to contain mutations that cause an autosomal dominant form of cone-rod dystrophy. This means that only one parent has to pass on the **gene mutation** in order for the child to be affected with the disease. This genetic form of CRD is clinically known as CORD2, or cone-rod dystrophy 2. Mutations in the CRX gene interfere in the development process of embryonic photoreceptor cells during the early stages of life. The result is abnormal photoreceptor cells with reduced function.

Demographics

Inherited retinal degeneration dystrophies have an incidence of approximately one in 4,000 people. Cone-rod dystrophy is an uncommon entity. The prevalence is estimated to be in the range of one in 10,000 to one in 100,000.

Signs and symptoms

The earliest symptom of CRD is loss of night vision that usually begins after the age of 20. The vision loss is progressive and unrelenting. Over the next decade, loss of all vision begins and by age 50, most people with cone-rod dystrophy have gone completely blind.

Cone-rod dystrophy is occasionally accompanied by amelogenesis imperfecta, which is characterized by abnormally shaped teeth and abnormalities in the tooth enamel.

Diagnosis

The earliest symptom of cone-rod dystrophy is decreased visual acuity. However, the diagnosis of cone-rod dystrophy is usually established with loss of the peripheral visual fields. Cone-rod dystrophy must be distinguished from **retinitis pigmentosa** (RP). In CRD, rods and cones are lost at approximately the same rate. It is further distinguished from RP by the absence of night blindness as a presenting symptom.

Treatment and management

As of 2001, there are no known treatments or cures for cone-rod dystrophy. It has been suggested, however, that people with cone-rod dystrophy may be able to slow the progression of their blindness by wearing sunglasses and avoiding bright light.

KEY TERMS

Amelogenesis imperfecta—A hereditary dental defect characterized by discoloration of the teeth.

Cones—Receptor cells that allow the perception of colors.

Nystagmus—Involuntary, rhythmic movement of the eye.

Photophobia—An extreme sensitivity to light.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Rod—Photoreceptor that is highly sensitive to low levels of light and transmits images in shades of gray.

Prognosis

Studies of individuals thought to have cone-rod dystrophy reveal that central vision loss begins in the first decade of life with the onset of night blindness occurring sometime after age 20. Little visual function remains after the age of 50. There is no cure for this syndrome.

Resources

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ORGANIZATIONS

American Academy of Ophthalmology. PO Box 7424, San Francisco, CA 94120-7424. (415) 561-8500. <http://www.eyenet.org>.

Association for Macular Diseases, Inc. 210 East 64th St., New York, NY 10021. (212) 605-3719. 2020@nei.nih.gov. <http://www.macula@macula.org>.

Foundation Fighting Blindness. Executive Plaza 1, 11350 McCormick Rd, Suite 800, Hunt Valley, MD 21031. (888) 394-3937. jchader@blindness.org. <http://www.blindness.org>.

National Eye Institute. 31 Center Dr., Bldg. 31, Rm 6A32, MSC 2510, Bethesda, MD 20892-2510. (301) 496-5248. 2020@nei.nih.gov. <http://www.nei.nih.gov>.

Retinitis Pigmentosa International. 23241 Ventura Blvd., Suite 117, Woodland Hills, CA 91364. (818) 992-0500 or (800) 344-4877. rpint@pacbell.net. <http://www.rpinternational.org>.

WEBSITES

Foundation Fighting Blindness: <*http://www.blindness.org/html/science/wcord2.html*>.

Retina Foundation of the Southwest. <http://www.retinafoundation.org/eyeinfo2.html>.

Southeastern Eye Center. <http://www.southeasterneyecenter.com/cases/bulls_eye.htm>.

L. Fleming Fallon, Jr, MD, DrPH

Congenital adrenal hyperplasia

Definition

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive genetic conditions that result from an abnormality in one of the enzymes required by the adrenal glands to convert cholesterol into cortisol, aldosterone, and androgens.

Description

The first likely description of congenital adrenal hyperplasia (CAH) occurred in 1865 when an anatomist named Luigi De Crecchio reported on a cadaver who had what appeared to be a penis with the urinary opening on its underside and undescended testicles. What was remarkable about this cadaver was that it also had a vagina, a uterus, fallopian tubes, ovaries and very enlarged adrenal glands. From four years of age until his death, this person had lived his life as a male although at birth he was declared a female. He died in his 40s after many episodes of vomiting, diarrhea, and prostration. This genetic female with masculinized external genitals and abnormalities in regulating the amount of salt in her body had all the symptoms of a textbook case of a severe and untreated CAH.

Congenital adrenal hyperplasia (CAH), formerly called adrenogenital syndrome, results from an abnormality in one of the enzymes required by the adrenal glands to convert cholesterol into cortisol, aldosterone, and androgens such as testosterone. These three hormones are very necessary for normal health. Cortisol helps the body to cope with stress such as injury or illness, aldosterone helps to insure that the body retains normal amounts of salt, and androgens such as testos-

terone are involved in the production of masculine traits such as body hair and the development of male sex organs.

There are many different enzymes necessary for the normal production of cortisol, aldosterone, and testosterone. Each type of CAH results from a deficiency in one of these enzymes. One of the most important enzymes involved in the breakdown of cholesterol is 21-hydroxylase. 21-hydroxylase is involved in the conversion of cholesterol to cortisol and aldosterone but is not involved in the conversion of cholesterol to testosterone. Ninety to ninety-five percent of people with CAH have a deficiency or absence of 21-hydroxylase (21-hydroxylase deficiency).

A deficiency or absence of 21-hydroxylase (CAH21) results in the production of decreased levels of cortisol and aldosterone, which prompts the body to compensate by forcing the adrenal glands to increase the conversion of cholesterol. This does not result in significantly increased levels of cortisol and aldosterone, but does result in increased levels of testosterone, which is produced by another enzyme. Both men and women normally produce some testosterone, although men typically produce larger amounts of this hormone.

Increased levels of testosterone can result in premature puberty in males and females and can cause the absence of a menstrual period and increased amounts of body hair in women. Females who produce high levels of this hormone in utero can be born with masculinized external genitals. Decreased levels of cortisol can also result in increased levels of two other hormones called 17-hydroxyprogesterone and androstenedione. Increased levels of 17-hydroxyprogesterone in conjunction with decreased levels of aldosterone can result in an inability of the body to retain normal amounts of salt.

The three major types of 21-hydroxylase deficiency (CAH21) are: (1) the classic salt-losing form, (2) the classic non-salt-losing form, and (3) the non-classical form (later onset form). The classic forms of the disorder, if untreated, can result in premature puberty in boys and can cause girls to be born with an enlarged clitoris or external male genitals. Men and women with untreated classical CAH21 can have increased growth in childhood but short adult height. The salt-losing form of CAH21 results in reduced levels of salt in the body, which can sometimes result in an adrenal crisis. An adrenal crisis is a life threatening condition characterized by severe dehydration, very low blood pressure, and vomiting. The non-classic form, which is milder and has a later onset, can cause women to have an absence of menstruation and increased body hair and can cause a low sperm count in men.

Genetic profile

All types of CAH are autosomal recessive genetic conditions. An autosomal recessive condition is caused by a change in both genes of a pair. A person with CAH, has changes in both copies of the **gene** responsible for producing one of the enzymes involved in the breakdown of cholesterol. He or she has inherited one changed gene from his or her mother and one changed gene from his or her father. CAH21 results from changes in a gene, called CYP21, which creates the enzyme 21-hydroxylase, and is found on chromosome 6. When the CYP21 gene is changed it does not produce any 21-hydroxylase or it produces small amounts of this enzyme. There are a number of different types of gene changes that can result in reduced levels of 21-hydroxylase. The amount of 21-hydroxylase produced depends on the type and combination of CYP21 gene changes and partially determines the severity of CAH21.

Parents who have a child with CAH are called carriers, since they each possess one changed CAH gene and one unchanged CAH gene. Carriers usually do not have any symptoms since they have one unchanged gene that produces enough enzyme to prevent the symptoms of CAH. Each child born to parents who are both carriers for the same type of CAH, has a 25% chance of having CAH, a 50% chance of being a carrier, and a 25% chance of being neither a carrier nor affected with CAH disease.

Demographics

Approximately one in 10,000 infants is born with CAH, making it the most common disorder of the adrenal glands. CAH affects both females and males of all ethnic backgrounds. CAH21 is the most common form of CAH affecting 90–95% of people with CAH. Approximately one in 60 people are carriers for CAH21.

Signs and symptoms

The type of symptoms experienced by a person with CAH depends on their particular enzyme deficiency. CAH can cause congenital masculinization of the female external genitals or can cause feminization of the male genitals. CAH does not, however, affect the internal sexual organs of either males or females. CAH can cause women to have an absence of menstrual periods and increased body hair and is associated with premature puberty in both males and females. In some cases CAH can result in an inability of the body to retain normal amounts of salt.

CAH21 has a range of symptoms and the severity of the disorder is partially related to the amount of 21-hydroxylase that the body produces. The three major

KEY TERMS

Adrenal gland—A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Carrier testing—Testing performed to determine if someone possesses one changed copy and one unchanged copy of a particular gene.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Congenital—Refers to a disorder that is present at birth.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Diagnostic testing—Testing performed to determine if someone is affected with a particular disease.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

In utero—While in the uterus; before birth.

Labia—Lips of the female genitals.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

types of 21-hydroxylase deficiency (CAH21) are: (1) the classic salt-losing form, (2) the classic non-salt-losing form, and (3) the non-classical form (later onset form).

Classic salt-losing form of CAH21

The classic salt-losing form is the most severe form of CAH21 and results when very little or no 21-hydroxylase is produced. Untreated girls may be mistaken for boys at birth since they are typically born with fairly masculinized external genitals. Their internal sexual organs are, however, normal. Males with untreated CAH21 have normal external genitals but may experience premature puberty. Signs of puberty such as pubic hair, enlarged penis, deepened voice, and increased muscle strength can occur long before normal puberty and can sometimes occur as early as two to three years of age. This form of CAH21, if untreated, results in a loss of salt that can trigger an adrenal crisis. An adrenal crisis is a life-threatening condition characterized by severe dehydration, very low blood pressure, weakening of the heart muscles, and vomiting. The adrenal crisis typically occurs by six to twelve weeks. On occasion, salt loss is not noticed until precipitated by an infection in early childhood. This form of CAH21, if untreated, can also cause increased growth in childhood but short adult height in men and women.

Classical non-salt-losing form of CAH21

The classical non-salt-losing form of CAH21 results when a low amount of 21-hydroxylase is produced. In

this form of CAH21 enough enzyme is present to prevent abnormally low levels of salt in the body and to prevent an adrenal crisis. Girls are born with slightly masculinized external genitals such as an enlarged clitoris and a partial fusion of the labia. If untreated, they may also experience early puberty and the lack of a menstrual period. Untreated boys have normal genitals but may have premature puberty. This form of CAH21, can also cause increased growth in childhood but short adult height in men and women.

Non-classical form of CAH21

The non-classical form is the mildest form of CAH21 and results from mildly decreased levels of 21-hydroxylase. Males and females with this form of CAH21 appear normal at birth and do not suffer from a deficiency of salt. Untreated women may have an increase in body hair, irregular or absent menstrual periods, and may have cysts on their ovaries. Many men do not have any symptoms even if untreated. Some men and woman have short stature, severe acne, and decreased fertility.

Diagnosis

Diagnostic testing

Most forms of CAH can be diagnosed by measuring the amount of specific hormones in a urine sample. The type of hormone that is found in excess amounts in the urine depends on the type of CAH. CAH21 can be diagnosed by measuring the amount of 17-hydroxyprogesterone in a urine sample since people with CAH21 typically have elevated amounts of this hormone in their urine.

CAH21 is however, best diagnosed through a blood test called an ACTH (adrenocorticotropic hormone) stimulation test. ACTH is a hormone that stimulates the adrenal glands to convert cholesterol to cortisol. The ACTH stimulation test measures the amount of 17-hydroxyprogesterone in the blood before and after stimulation with ACTH. People with CAH21 have an exaggerated production of 17-hydroxyprogesterone after stimulation with ACTH. The ACTH stimulation test can usually identify what type of CAH21 a person is affected with.

Once a biochemical diagnosis of CAH is made, DNA testing may be recommended. DNA testing is available for some but not all types of CAH. Detection of a CYP21 gene alteration in a person with CAH21 can confirm an uncertain diagnosis and can help facilitate prenatal diagnosis and carrier testing of relatives. Some people with CAH21 may possess DNA changes that are not detectable through DNA testing.

Carrier testing

A person who has a relative with CAH or parents who have a child with CAH21 should consider undergoing carrier testing. Carriers for CAH21 can sometimes be identified through the ACTH stimulation test, although DNA testing is more accurate and is usually the recommended test. If possible, DNA testing should be first performed on the family member who is affected with CAH21. If a change in the CYP21 gene is detected, then carrier testing can be performed in relatives such as siblings and parents, with an accuracy of greater than 99%. If the affected relative does not possess detectable CYP21 gene changes, then DNA carrier testing will be inaccurate and should not be performed. In these cases ACTH stimulation testing of the potential carrier can be considered. If DNA testing of the affected relative cannot be performed, DNA carrier testing of family members can still be performed but will only identify approximately 95% of carriers.

Carrier testing should also be considered by someone who has a partner who is a carrier or is affected with CAH. DNA testing, which identifies approximately 95% of carriers for CAH21, is the recommended test for people who choose to undergo carrier testing but who do not themselves have a family history of CAH21.

Prenatal testing

If both parents are carriers for the same type of CAH or one parent is a carrier for CAH and one parent is affected with the same type of CAH, then prenatal testing should be considered. Prenatal testing is available for CAH21 and some of the other types of CAH. DNA testing is the recommended method of prenatal testing for CAH21 but it can only be performed if both parents have detectable mutations (gene changes) in CYP21. Prenatal testing cannot always identify what type of CAH21 a fetus has.

Some parents are known to be carriers for CAH21 since they already have a child with CAH21, yet they do not possess CYP21 gene changes that are detectable through DNA testing. Prenatal diagnosis can be performed in these cases by measuring the amount of 17-hydroxyprogesterone in the amniotic fluid, obtained from an **amniocentesis**. This type of prenatal testing can only detect the salt-losing form of CAH21.

Prenatal testing is especially important for mothers who are undergoing dexamethasone therapy to help prevent their daughters from being born with masculine genitalia. Although treatment must be started before prenatal testing can be performed, treatment can be discontinued if the baby is found to be a male or female who does not have CAH21.

Newborn screening

Many states offer newborn screening for CAH21. If newborn screening is available in your state, then hospitals in that state will automatically screen for CAH21 by measuring the amount of 17-hydroxyprogesterone in a drop of blood obtained from a newborn baby. More precise testing should be done if the initial test indicates that an infant has CAH21.

Treatment and management

Medications

Most people with CAH are treated with cortisol-like medications and in most cases this therapy is life-long. The goal of treatment is to return cortisol, aldosterone, and testosterone to near normal levels. People with the salt-losing and non-salt-losing forms of CAH21 are treated with injections of cortisol-like steroid medications or oral steroid medications. People with the salt-losing form are also given a form of oral aldosterone. Babies with the salt-losing form of CAH21 need to have salt added to their formula or breast milk. Children and adults do not need a salt supplement provided they have a high salt diet. An adrenal crisis is treated by intravenous administration of fluids containing sugars and salt. People with the non-classical form of CAH21, who require treatment, are treated with oral steroids. Medical therapy achieves hormonal balance most of the time, but CAH patients can have periods of fluctuating hormonal control. These fluctuations often require modifications in the amount of steroid required for treatment.

Some people with the salt-losing form of CAH21 are resistant to standard therapy. As of 2001, the National Institutes of Health is conducting clinical trials determining the efficacy of a new combination drug treatment for CAH21. This experimental therapy involves treatment with a combination of four medications—flutamide, testolactone, reduced hydrocortisone dose, and fludrocortisone. The goal of these trials is to see whether this type of medical therapy is able to effectively treat CAH21 and still allow treated individuals to obtain a normal adult stature. Preliminary results are encouraging, but further research trials are necessary before the safety and effectiveness of this therapy is fully known.

Surgery

Adrenalectomy, a surgical procedure to remove the adrenal glands, is a more radical treatment for people with the salt-losing form of CAH21 who have little or no enzyme activity. This surgery allows people with CAH21 to be treated with lower dose steroids.

Girls born with masculinized genitals may undergo a surgery to create female genitals. This surgery is often performed at about six to twelve weeks of age. Sometimes an initial surgery is performed at that time followed by a surgery to correct the opening to the vagina when the girl becomes sexually active. Some people believe that any genital surgery should be delayed until the individual is old enough to decide whether they want the surgery.

Prenatal treatment

Some mothers who are at risk for having a child with CAH21 choose to take a type of steroid called dexamethasone while they are pregnant. This treatment can often prevent the masculinization of external genitals in female fetuses. To be fully effective this treatment needs to be started at approximately five to six weeks of gestation prior to the formation of the external genitals. Treatment can be stopped if prenatal testing finds that the baby is male or is an unaffected female, otherwise treatment continues until birth. Although this treatment does not appear to have many adverse effects on the fetus, the long-term risks are not known. The mother may, however, experience side effects such as weight gain, fluid accumulation, sugar intolerance, high blood pressure, gastrointestinal problems, and mood swings.

Prognosis

If appropriately treated, the prognosis for CAH and particularly CAH21 is good and most people have a normal lifespan. The prognosis for patients with the salt-losing form of CAH21 is, however, dependent on early identification and treatment. Some women and men with CAH 21, even if treated, have a short adult stature and may have decreased fertility. Women surgically treated for masculinized genitals may experience physical and/or psychological difficulties with sexual intercourse. They may also experience gender confusion and sexual identity difficulties.

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Ambiguous Genitalia Support Network. PO Box 313, Clements, CA 95227-0313. (209) 727-0313. Fax: (209) 727-0313. agsn@jps.net. <http://www.stepstn.com>.

Congenital Adrenal Hyperplasia <http://congenitaladrenalhyperplasia.org>.

National Adrenal Diseases Foundation. 510 Northern Blvd., Great Neck, NY 11021. (516) 487-4992. <http://medhlp.netusa.net/www/nadf.htm>.

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Lisa Andres, MS, CGC

Congenital contractural arachnodactyly *see* **Beals syndrome**

Congenital familial hypertrophic synovitis *see* **Arthropathy-camptodactyly syndrome**

Congenital heart disease

Definition

Congenital heart disease, also called congenital heart defect, includes a variety of malformations of the heart or its major blood vessels that are present at the birth of a child.

Description

Congenital heart disease occurs when the heart or blood vessels near the heart do not develop properly before birth. Some infants are born with mild types of congenital heart disease, but most need surgery in order to survive. Patients who have had surgery are likely to experience other cardiac problems later in life.

Most types of congenital heart disease obstruct the flow of blood in the heart or the nearby vessels, or cause an abnormal flow of blood through the heart. Rarer types of congenital heart disease occur when the newborn has only one ventricle, when the pulmonary artery and the aorta come out of the same ventricle, or when one side of the heart is not completely formed.

Patent ductus arteriosus

Patent ductus arteriosus refers to the opening of a passageway—or temporary blood vessel (ductus)—to carry the blood from the heart to the aorta before birth, allowing blood to bypass the lungs, which are not yet functional. The ductus should close spontaneously in the first few hours or days after birth. When it does not close in the newborn, some of the blood that should flow through the aorta then returns to the lungs. Patent ductus arteriosus is common in premature babies, but rare in full-term babies. It has also been associated with mothers who had German measles (rubella) while pregnant.

Hypoplastic left heart syndrome

Hypoplastic left heart syndrome, a condition in which the left side of the heart is underdeveloped, is rare, but it is the most serious type of congenital heart disease. With this syndrome, blood reaches the aorta, which pumps blood to the entire body, only from the ductus, which then normally closes within a few days of birth. In hypoplastic left heart syndrome, the baby seems normal at birth, but as the ductus closes, blood cannot reach the aorta and circulation fails.

Obstruction defects

When heart valves, arteries, or veins are narrowed, they partly or completely block the flow of blood. The most common obstruction defects are pulmonary valve stenosis, aortic valve stenosis, and coarctation of the aorta. **Bicuspid aortic valve** and subaortic stenosis are less common.

Stenosis is a narrowing of the valves or arteries. In pulmonary stenosis, the pulmonary valve does not open properly, forcing the right ventricle to work harder. In aortic stenosis, the improperly formed aortic valve is nar-

rowed. As the left ventricle works harder to pump blood through the body, it becomes enlarged. In coarctation of the aorta, the aorta is constricted, reducing the flow of blood to the lower part of the body and increasing blood pressure in the upper body.

A bicuspid aortic valve has only two flaps instead of three, which can lead to stenosis in adulthood. Subaortic stenosis is a narrowing of the left ventricle below the aortic valve, which limits the flow of blood from the left ventricle.

Septal defects

When a baby is born with a hole in the septum (the wall separating the right and left sides of the heart), blood leaks from the left side of the heart to the right, or from a higher pressure zone to a lower pressure zone. A major leakage can lead to enlargement of the heart and failing circulation. The most common types of septal defects are atrial septal defect, an opening between the two upper heart chambers, and ventricular septal defect, an opening between the two lower heart chambers. Ventricular septal defect accounts for about 15% of all cases of congenital heart disease in the United States.

Cyanotic defects

Heart disorders that cause a decreased, inadequate amount of oxygen in blood pumped to the body are called cyanotic defects. Cyanotic defects, including truncus arteriosus, total anomalous pulmonary venous return, tetralogy of Fallot, transposition of the great arteries, and tricuspid atresia, result in a blue discoloration of the skin due to low oxygen levels. About 10% of cases of congenital heart disease in the United States are tetralogy of Fallot, which includes four defects. The major defects are a large hole between the ventricles that allows oxygen-poor blood to mix with oxygen-rich blood, and narrowing at or beneath the pulmonary valve. The other defects are an overly muscular right ventricle and an aorta that lies over the ventricular hole.

In transposition (reversal of position) of the great arteries, the pulmonary artery and the aorta are reversed, causing oxygen-rich blood to re-circulate to the lungs while oxygen-poor blood goes to the rest of the body. In tricuspid atresia, the baby lacks a triscupid valve and blood cannot flow properly from the right atrium to the right ventricle.

Other defects

Ebstein's anomaly is a rare congenital syndrome that causes malformed tricuspid valve leaflets, which allow blood to leak between the right ventricle and the right atrium. It also may cause a hole in the wall between the left and right atrium. Treatment often involves repairing the tricuspid valve. Ebstein's anomaly may be associated with maternal use of the psychiatric drug lithium during pregnancy.

Brugada syndrome is another rare congenital heart defect that appears in adulthood and may cause sudden death if untreated. Symptoms, which include rapid, uneven heart beat, often appear at night. Scientists believe that Brugada syndrome is caused by mutations in the **gene** SCN5A, which involves cardiac sodium channels.

Infants born with DiGeorge sequence can have heart defects such as a malformed aortic arch and tetralogy of Fallot. Researchers believe DiGeorge sequence

KEY TERMS

Aorta—The main artery located above the heart which pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

Congenital—Refers to a disorder which is present at birth.

Cyanotic—Marked by bluish discoloration of the skin due to a lack of oxygen in the blood. It is one of the types of congenital heart disease.

Ductus—The blood vessel that joins the pulmonary artery and the aorta. When the ductus does not close at birth, it causes a type of congenital heart disease called patent ductus arteriosus.

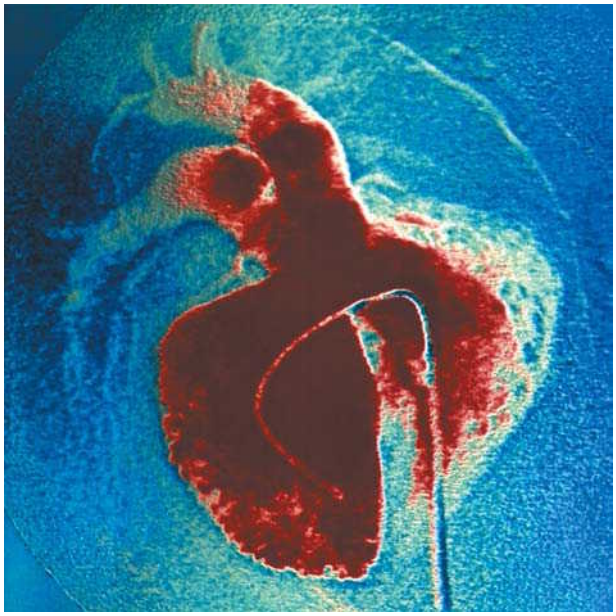
Electrocardiograph (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Hypoplastic—Incomplete or underdevelopment of a tissue or organ. Hypoplastic left heart syndrome is the most serious type of congenital heart disease.

Neuchal translucency—A pocket of fluid at the back of an embryo's neck visible via ultrasound that, when thickened, may indicate the infant will be born with a congenital heart defect.

Septal—Relating to the septum, the thin muscle wall dividing the right and left sides of the heart. Holes in the septum are called septal defects.

Stenosis—The constricting or narrowing of an opening or passageway.



An angiogram showing a hole in the heart of a young patient. *(Photo Researchers, Inc.)*

is most often caused by mutations in genes in the region 22q11.

Marfan syndrome is a connective tissue disorder that causes tears in the aorta. Since the disease also causes excessive bone growth, most Marfan syndrome patients are over six-feet-tall. In athletes, and others, it can lead to sudden death. Researchers believe the defect responsible for Marfan syndrome is found in gene FBN1, on chromosome 15.

Genetic profile

Scientists have made much progress in identifying some of the genes that are responsible for congenital heart defects, but others remain a mystery. When possible, **genetic testing** can help families determine the risk that their child will be born with a heart defect.

Demographics

About 32,000 infants are born every year with congenital heart disease, which is the most common birth defect. About half of these patients will require medical treatment. More than one million people with heart defects are currently living in the United States.

Signs and symptoms

In most cases, the causes of congenital heart disease are unknown. Genetic and environmental factors, and lifestyle habits can all be involved. The likelihood of having a child with a congenital heart disease increases if the mother or father, another child, or another relative had congenital heart disease or a family history of sudden death. Viral infections, such as German measles, can produce congenital heart disease. Women with diabetes and phenylketonuria also are at higher risk of having children with congenital heart defects. Many cases of congenital heart disease result from the mother's excessive use of alcohol or illegal drugs, such as cocaine, while pregnant. The mother's exposure to certain anticonvulsant and dermatologic drugs during pregnancy can also cause congenital heart disease. There are many genetic conditions, such as Down syndrome, which affect multiple organs and can cause congenital heart disease.

Symptoms of congenital heart disease in general include: shortness of breath, difficulty feeding in infancy, sweating, cyanosis (bluish discoloration of the skin), heart murmur, respiratory infections that recur excessively, stunted growth, and limbs and muscles that are underdeveloped.

Symptoms of specific types of congenital heart disease are as follows:

- Patent ductus arteriosus: quick tiring, slow growth, susceptibility to pneumonia, rapid breathing. If the ductus is small, there are no symptoms.
- Hypoplastic left heart syndrome: ashen color, rapid and difficult breathing, inability to eat.
- Obstruction defects: cyanosis (skin that is discolored blue), chest pain, tiring easily, dizziness or fainting, congestive heart failure, and high blood pressure.
- Septal defects: difficulty breathing, stunted growth. Sometimes there are no symptoms.
- Cyanotic defects: cyanosis, sudden rapid breathing or unconsciousness, and shortness of breath and fainting during exercise.

Diagnosis

Echocardiography and cardiac magnetic resonance imaging are used to confirm congenital heart disease when it is suggested by the symptoms and physical examination. An echocardiograph will display an image of the heart that is formed by sound waves. It detects valve and other heart problems. Fetal echocardiography is used to diagnose congenital heart disease in utero, usually after 20 weeks of pregnancy. Between 10 and 14 weeks of pregnancy, physicians also may use an ultrasound to look for a thickness at the nuchal translucency, a pocket of fluid in back of the embryo's

neck, which may indicate a cardiac defect in 55% of cases. Cardiac magnetic resonance imaging, a scanning method that uses magnetic fields and radio waves, can help physicians evaluate congenital heart disease, but is not always necessary. Physicians may also use a chest x ray to look at the size and location of the heart and lungs, or an electrocardiograph (ECG), which measures electrical impulses to create a graph of the heart beat.

Treatment and management

Congenital heart disease is treated with drugs and/or surgery. Drugs used include diuretics, which aid the baby in excreting water and salts, and digoxin, which strengthens the contraction of the heart, slows the heartbeat, and removes fluid from tissues.

Surgical procedures seek to repair the defect as much as possible and restore circulation to as close to normal as possible. Sometimes, multiple surgical procedures are necessary. Surgical procedures include: arterial switch, balloon atrial septostomy, balloon valvuloplasty, Damus-Kaye-Stansel procedure, Fontan procedure, pulmonary artery banding, Ross procedure, shunt procedure, and venous switch or intra-atrial baffle.

Arterial switch, to correct transposition of the great arteries, involves connecting the aorta to the left ventricle and connecting the pulmonary artery to the right ventricle. Balloon atrial septostomy, also done to correct transposition of the great arteries, enlarges the atrial opening during heart catheterization. Balloon valvuloplasty uses a balloon-tipped catheter to open a narrowed heart valve, improving the flow of blood in pulmonary stenosis. It is sometimes used in aortic stenosis. Transposition of the great arteries can also be corrected by the Damus-Kaye-Stansel procedure, in which the pulmonary artery is cut in two and connected to the ascending aorta and the farthest section of the right ventricle.

For tricuspid atresia and pulmonary atresia, the Fontan procedure connects the right atrium to the pulmonary artery directly or with a conduit, and the atrial defect is closed. Pulmonary artery banding, narrowing the pulmonary artery with a band to reduce blood flow and pressure in the lungs, is used for ventricular septal defect, atrioventricular canal defect, and tricuspid atresia. Later, the band can be removed and the defect corrected with open-heart surgery.

To correct aortic stenosis, the Ross procedure grafts the pulmonary artery to the aorta. For tetralogy of Fallot, tricuspid atresia, or pulmonary atresia, the shunt procedure creates a passage between blood vessels, sending blood into parts of the body that need it. For transposition of the great arteries, venous switch creates a tunnel inside the atria to re-direct oxygen-rich blood to the right ventricle and aorta and venous blood to the left ventricle and pulmonary artery.

When all other options fail, some patients may need a heart transplant. Children with congenital heart disease require lifelong monitoring, even after successful surgery. The American Heart Association recommends regular dental check-ups and the preventive use of antibiotics to protect patients from heart infections, or endocarditis. Since children with congenital heart disease have slower growth, nutrition is important. Physicians may also limit their athletic activity.

Prognosis

The outlook for children with congenital heart disease has improved markedly in the past two decades. Many types of congenital heart disease that would have been fatal can now be treated successfully. Research on diagnosing heart defects when the fetus is in the womb may lead to future treatment to correct defects before birth. Promising new prevention methods and treatments include genetic screening and the cultivation of cardiac tissue in the laboratory that could be used to repair congenital heart defects.

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American Heart Association. 7272 Greenville Ave., Dallas, TX 75231-4596. (214) 373-6300 or (800) 242-8721. inquire @heart.org. <http://www.americanheart.org>.

Congenital Heart Disease Information and Resources. 1561 Clark Dr., Yardley, PA 19067. <http://www.tchin.org>.

Texas Heart Institute Heart Information Service. PO Box 20345, Houston, TX 77225-0345. (800) 292-2221. <http://www.tmc.edu/thi/his.html>.

Melissa Knopper

Congenital hypothyroid syndrome

Definition

Congenital hypothyroid syndrome is a condition in which a child is born with a deficiency in thyroid gland activity or thyroid hormone levels.

Description

The thyroid gland is a small gland in the front of the neck that secretes thyroid hormones called thyroxine (T4) and triiodothyronine (T3) into the bloodstream. Some of the T4 is converted into T3 by the liver and kidney. These thyroid hormones help regulate a great number of processes. A deficiency in the level of these hormones can affect the brain, heart, muscles, skeleton, digestive tract, kidneys, reproductive function, blood cells, other hormone systems, heat production, and energy metabolism.

In most cases of congenital hypothyroidism, the thyroid gland is either completely absent or severely underdeveloped. Sometimes thyroid tissue is located in ectopic, or abnormal, locations along the neck.

Other abnormalities can lead to congenital hypothyroidism including:

- abnormal synthesis of thyroid hormones;
- abnormal synthesis of thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone (TRH), which are regulatory hormones that affect the production of thyroid hormones;
- abnormal response to thyroid hormones, TSH or TRH;
- inadvertent administration of harmful drugs or substances to the pregnant mother, possibly resulting in temporary congenital hypothyroidism in the newborn;
- dietary deficiency of iodine, a raw component vital to the manufacture thyroid hormones.

Genetic profile

Most causes of congenital hypothyroidism are not inherited. Some abnormalities in thyroid hormone synthesis (TSH synthesis), or the response to TSH, are inherited in autosomal recessive fashion. This means that both parents have one copy of the changed (mutated) **gene** but do not have the condition. Abnormal response to thyroid hormone may be an autosomal dominant condition, meaning that only one parent has to pass on the **gene mutation** in order for the child to be affected with the syndrome.

KEY TERMS

Congenital—Refers to a disorder which is present at birth.

Ectopic—Tissue found in an abnormal location.

Hypothyroid—Deficiency in thyroid gland activity or thyroid hormone levels.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Levothyroxine—A form of thyroxine (T4) for replacement of thyroid hormones in hypothryoidism.

Myxedema—Swelling of the face, hands, feet, and genitals due to hypothyroidism.

Scintigraphy—Injection and detection of radioactive substances to create images of body parts.

Thyroxine (T4)—Thyroid hormone.

Triiodothyronine (T3)—Thyroid hormone.

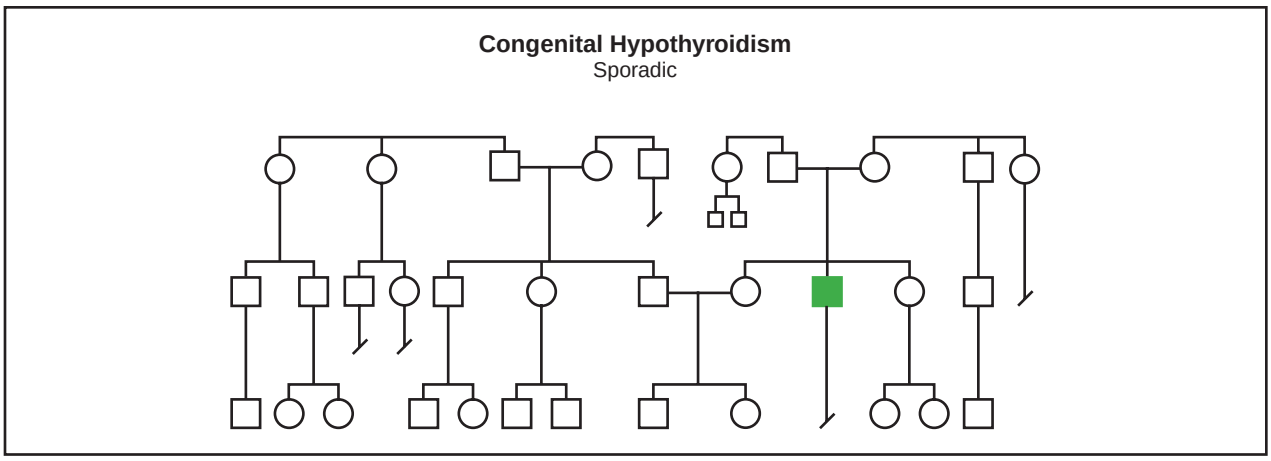
Demographics

Congenital hypothyroidism occurs in one in every 4,000 newborns in the United States. It is twice as common in girls as in boys. The condition is less common in African Americans and more common in Hispanics and Native Americans.

Signs and symptoms

The signs and symptoms of congenital hypothyroidism are difficult to observe because the mother passes along some of her thyroid hormones to the fetus during pregnancy. Even if the newborn is completely lacking a thyroid gland, it may not be obvious in the early stages of life. Ectopic thyroid tissue may also provide enough thyroid hormones for a short period of time.

Rarely, the affected newborn will exhibit jaundice (yellow skin), noisy breathing, and enlarged tongue. If hypothyroidism continues undetected and untreated, the infant may gradually demonstrate feeding problems, constipation, sluggishness, sleepiness, cool hands and feet, and failure to thrive. Other signs include protruding abdomen, slow pulse, enlarged heart, dry skin, delayed teething, and coarse hair. Affected children may also have myxedema, which is swelling of the face, hands, feet, and genitals. Hypothyroidism eventually leads to marked retardation in physical growth, mental development, and sexual maturation.



(Gale Group)

Diagnosis

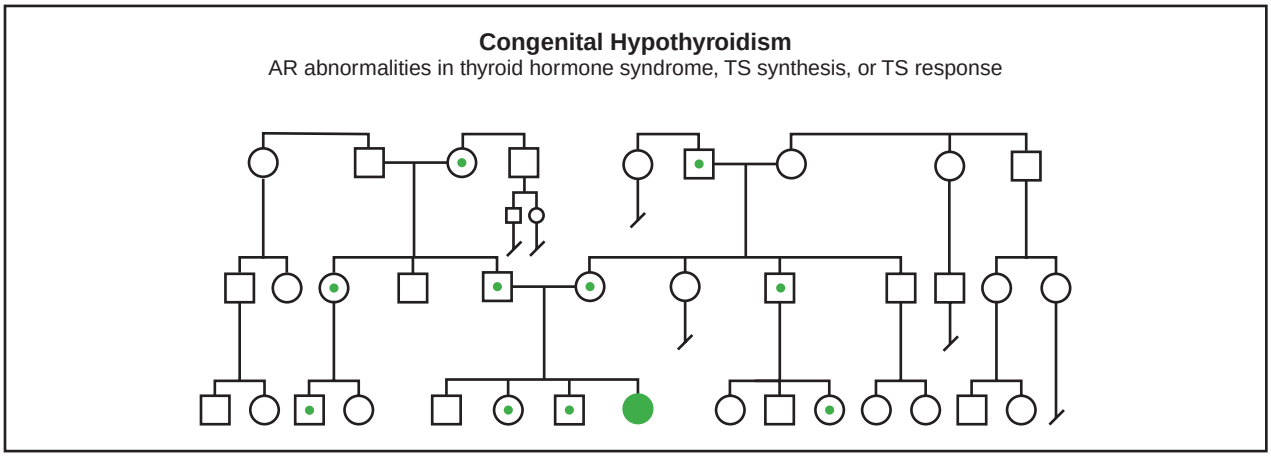
Prompt diagnosis and treatment are critical to avoid the profound consequences of hypothyroidism. The signs and symptoms of hypothyroidism are often subtle in newborns, only to manifest themselves later in life when permanent damage has been done. Before the implementation of screening for hypothyroidism in the 1970s, most children with the disease suffered growth and mental retardation, as well as neurological and psychological deficits.

Most cases of congenital hypothyroid syndrome are now detected by a screening test performed during a newborn's first few days of life. Every state offers testing, and most states require it. The test for hypothyroidism is part of a battery of standard screening tests designed to diagnose important conditions. A sample of the child's blood is analyzed for levels of thyroxine (T4), thyroid-stimulating hormone (TSH), or both, depending on the individual state or country. Some states also require a second round of screening performed one to four weeks later.

Once the diagnosis of congenital hypothyroidism is made, other tests can pinpoint the nature of the abnormality. X rays of the hip, shoulder, or skull often reveal characteristically abnormal patterns of bone development. Scintigraphy is a method by which images of the thyroid gland and any ectopic thyroid tissue are obtained to determine if the thyroid is absent or ectopic. But treatment should not be delayed for these other tests. Early treatment offers a good probability of normal development.

Treatment and management

Treatment of congenital hypothyroidism requires replacement of deficient thyroid hormones with levothyroxine, an oral tablet form of T4. There is no need to



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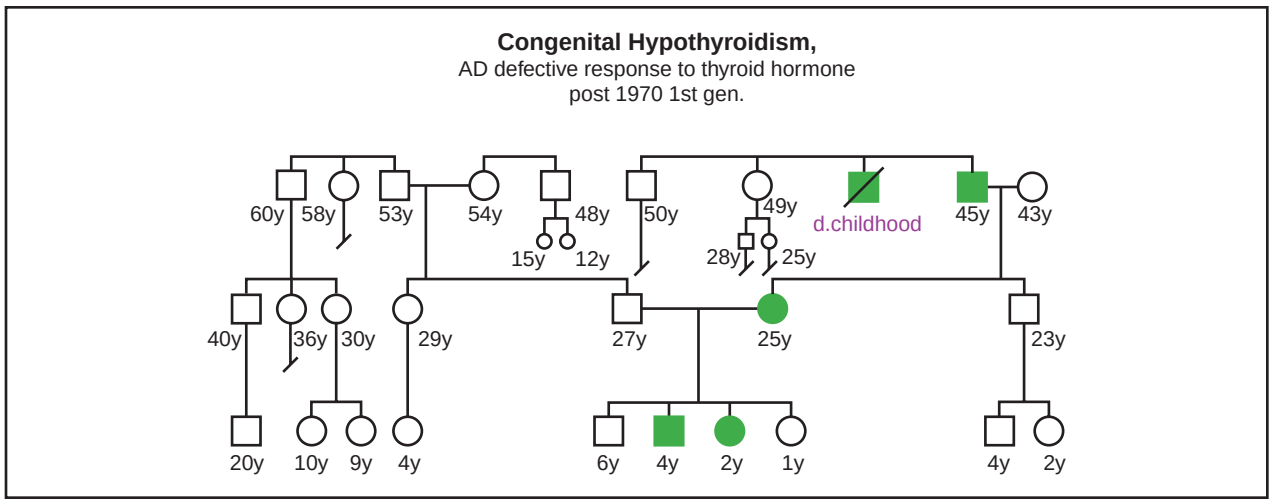

(Gale Group)

directly replace T3, since T4 is converted to T3 by the liver and kidney. Hypothyroid children usually require more levothyroxine per pound of body weight than hypothyroid adults do. The importance of prompt and adequate treatment cannot be overemphasized. Delays in treatment result in permanent stunting of physical, mental, and sexual development.

Blood levels of T4 should be checked regularly to ensure appropriate replacement. The blood levels of TSH should also be monitored since TSH is an indicator of the effectiveness of T4 replacement. As the child develops, the physical growth rate also provides a good measure of treatment.

Prognosis

If congenital hypothyroidism is detected and treated early in life, the prognosis is quite good. Most children will develop normally. However, the most severely affected infants may have mild mental retardation, speech difficulty, hearing deficit, short attention span, or coordination problems.

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Kevin O. Hwang, MD

Congenital ichthyosis-mental retardation-spasticity syndrome *see* **Sjögren Larsson syndrome**

Congenital isolated hemihypertrophy *see* **Hemihypertrophy**

Congenital megacolon *see* **Hirschsprung disease**

Congenital retinal blindness *see* **Leber amaurosis congenita**

Conjoined twins

Definition

Conjoined twins are an extremely rare type of identical twins who are physically joined at birth.

Description

Scientists believe conjoined twins form because of a delay in the fertilized egg's division. In normal identical

twins, the egg splits at four to eight days after fertilization. In conjoined twins, however, the split occurs sometime after day 13. Instead of forming two separate embryos, the twins remain partially attached as they develop inside the womb. In most cases, conjoined twins do not survive more than a few days past birth because of a high rate of malformed organs and other severe birth abnormalities. However, surgical separations have been successful in conjoined twins that have a superficial physical connection.

Conjoined twins are commonly referred to as Siamese twins, although this is now considered a derogatory term. The phrase Siamese twins originated from the famous conjoined twins Eng and Chang Bunker, who were born in Siam (Thailand) in 1811.

Some conjoined twins are attached at the upper body, others may be joined at the waist and share a pair of legs. Conjoined twins often share major organs such as a heart, liver, or brain. Medical experts have identified several types of conjoined twins. They are classified according to the place their bodies are joined. Most of the terms contain the word pagus, which means "fastened" in Greek.

Upper body

Cephalopagus: A rare form that involves conjoined twins with fused upper bodies and two faces on opposite sides of a single head.

Craniopagus: Conjoined twins with separate bodies and one shared head is a rare type and only occurs in 2% of cases.

Thoracopagus: About 35% of conjoined twin births have this common form of the condition, which joins the upper bodies. These twins usually share a heart, making surgical separation nearly impossible.

Lower body

Ischopagus: About 6% of conjoined twins are attached at the lower half of the body.

Omphalopagus: The type of conjoined twins that are attached at the abdomen and that often share a liver accounts for approximately 30% of all cases.

Parapagus: About 5% of conjoined twins are joined along the side of their lower bodies.

Pygopagus: About 19% of conjoined twins are joined back to back with fused buttocks.

Rare types

Dicephalus: Twins that share one body, but have two separate heads and necks.

KEY TERMS

Breech delivery—Birth of an infant feet or buttocks first.

Craniopagus—Conjoined twins with separate bodies and one shared head.

Dicephalus—Conjoined twins who share one body but have two separate heads and necks.

Fetus in fetu—In this case, one fetus grows inside the body of the other twin.

Ischopagus—Conjoined twins who are attached at the lower half of the body.

Omphalopagus—Conjoined twins who are attached at the abdomen.

Parapagus—Conjoined twins who are joined at the side of their lower bodies.

Parasitic twins—Occurs when one smaller, malformed twin is dependent on the larger, stronger twin for survival.

Pygopagus—Conjoined twins who are joined back to back with fused buttocks.

Thoracopagus—Conjoined twins joined at the upper body who share a heart.

Zygote—The cell formed by the uniting of egg and sperm.

Parasitic twins: This occurs when one smaller, malformed twin is dependent on the larger, stronger twin for survival.

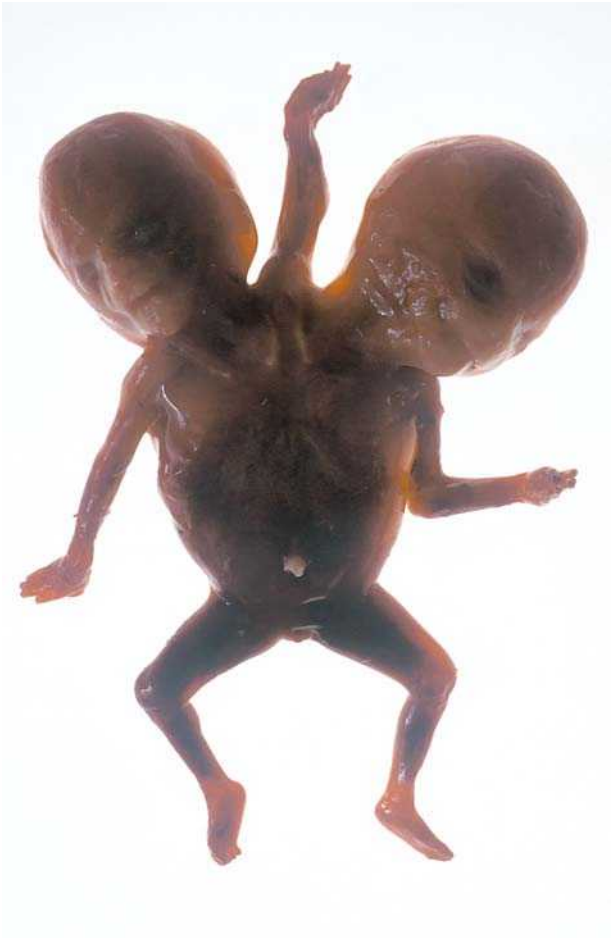
Fetus in fetu: In this unusual case, one fetus grows inside the body of the other twin.

Genetic profile

Scientists are still searching for the cause of conjoined twins. They believe a combination of genetic and environmental factors may be responsible for this rare condition.

Demographics

Conjoined twins occur in one out of every 50,000 births. Many such pregnancies are terminated before birth, or the infants are stillborn. Conjoined twins are always identical and of the same sex. They are more often female than male, by a ratio of 3:1. Conjoined twins are more likely to occur in Africa, India, or China than in the United States. Conjoined twins have appeared in triplet



These conjoined twins developed until the 17 week of pregnancy. It is difficult for conjoined twins to survive when they share the same key organs such as these siblings. *(Custom Medical Stock Photo, Inc.)*

and quadruplet births, but no cases of conjoined triplets or quadruplets have ever been reported. Most parents of conjoined twins are younger than 35 years old.

Signs and symptoms

Approximately 50% of women who are pregnant with conjoined twins will develop excess fluid surrounding the fetuses, which can lead to premature labor and an increased risk of miscarriage. Conjoined twins joined at the abdomen (omphalopagus) are more likely to be breech babies. In breech births, infants are born feet or buttocks first instead of head first. Most omphalopagus conjoined twins are born by cesarean section to increase their odds of survival.

Conjoined twins can be born with a complication called hydrops, which causes excessive fluid to build up in an infant's body and can be life-threatening. Those who survive past birth may experience congenital heart disease, liver or kidney disease, physical or mental disabilities, and intestinal blockages.

Diagnosis

Physicians typically try to determine if a woman is having conjoined twins at an early stage so that the parents can have an option to terminate the pregnancy if the odds of survival are low. Ultrasound imaging is a technique in which high-frequency sound waves create a picture of a developing fetus inside the womb and is often used to make the diagnosis. Initial diagnosis is possible at 10-12 weeks of gestation, but it is difficult to determine which body structures are involved until 20 weeks of gestation.

In utero, the three-dimensional magnetic resonance imaging (MRI) test is another important diagnostic tool that helps more precisely define which body parts of the conjoined twins are connected. An abdominal x ray of the mother is used to look for connected bones in conjoined twin embryos.

Treatment and management

Early diagnosis is key so that families and health-care providers can begin to plan for the birth of conjoined twins. Because of the high rate of miscarriage and difficult labor, most conjoined twins are delivered by cesarean section. Some conjoined twins have survived and lived full lives without serious medical interventions. If the twins do not share a large number of organs, however, physicians typically will recommend a surgical separation.

A large medical team must be assembled for a surgical separation. Physicians prefer to wait for a few months after birth, but that may not be possible if the twins are born with life-threatening congenital abnormalities. The type of surgery that is performed is determined by where the twins are connected. Doctors will often insert tissue expansion devices into the twins' skin before the operation to promote better healing at the site of separation.

Conjoined twins who survive a surgical separation will have many ongoing health-care needs, from wound care to prosthetic limbs and special diets. As the twins grow up and start school, they also may need counseling to help them adjust.

Prognosis

The majority of conjoined twin pregnancies are not successful. However, most conjoined twins who undergo a planned surgical separation several months after birth do survive. The survival rate for conjoined twins who need an emergency separation at birth is approximately 44%.

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Center for Study of Multiple Birth. 334 E. Superior St., Suite 464, Chicago, IL 60611. (312) 266-9093. <http://www.multiplebirth.com>.

Conjoined Twins International. PO Box 10895, Prescott, AZ 86304-0895.

National Organization of Mothers of Twins Clubs. PO Box 438, Thompson Station, TN 37179. (615) 595-0936. <http://www.nomotc.org>.

Twins Foundation. PO Box 6043, Providence, RI 02940-6043. (401) 751-8946. Twins@twinsfoundation.com.

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Melissa Knopper

Cooley's anemia *see* **Beta-thalassemia**

Corneal dystrophy

Definition

Corneal dystrophy is a condition that causes a layer of the cornea to cloud over and impair visual clarity. It is usually a bilateral problem, which means it occurs in both eyes equally. There are more than 20 different forms of inherited corneal dystrophies. A corneal dystrophy can occur in otherwise healthy individuals. Depending on the type of condition and the age of the individual, a corneal dystrophy may either cause no problems, moderate vision impairment, or severe difficulties that require surgery.

Description

The cornea is the outside layer of the eye, and comprises five layers itself, including the outer epithelium, the Bowman's layer, the stroma, or middle, layer that takes up about 90% of the entire cornea, the Descemet's membrane, and the endothelium. In most cases, the central (stromal) layer of the cornea is involved.

Some corneal dystrophies are named after the individual who discovered them, while others are descriptive of the pattern seen with the dystrophy or the location of the disease. The key forms of corneal dystrophy are congenital hereditary endothelial dystrophy (CHED), epithelial basement membrane dystrophy, Fuchs' endothelial dystrophy, granular dystrophy, lattice dystrophy, macular corneal dystrophy, Meesmann's corneal dystrophy, posterior polymorphous dystrophy (PPD), and Reis-Bucklers' dystrophy.

Genetic profile

Genetic alterations (mutations) causing corneal dystrophies have been mapped to 10 different **chromosomes**. Some dystrophies have not yet been mapped, including Fuchs' dystrophy.

Some corneal dystrophies have the same genetic address. Mutations on the BIGH3 **gene** of chromosome 5q31 cause granular corneal dystrophy and Reis-Bucklers' dystrophy. Macular corneal dystrophy has been mapped to an altered gene on chromosome 16. The mutation causing congenital hereditary endothelial dystrophy has been mapped to 20p11-20q11. Lattice type I is linked to the 5q31 locus (location), while lattice type II dystrophy is linked to the 9q34 locus. Posterior polymorphous corneal dystrophy has been linked to the 20q11 locus.

Most corneal dystrophies, with the exception of congenital endothelial corneal dystrophy and macular dystrophy, are autosomal dominant. In dominant disorders, a single copy of the mutated gene (received from either parent) dominates the normal gene and results in the appearance of the disease. The risk of transmitting the disorder from parent to offspring is 50% for each pregnancy.

Both congenital endothelial corneal dystrophy and macular dystrophy are autosomal recessive. This means the affected person inherits the same abnormal gene for the same trait from both parents; each parent is a carrier for the disease, but they usually will have no symptoms of the disease. The risk of transmitting the disease to each pregnancy is 25%.

KEY TERMS

Basement membrane—Part of the epithelium, or outer layer of the cornea.

Bowman's layer—Transparent sheet of tissue directly below the basement membrane.

Corneal transplant—Removal of impaired and diseased cornea and replacement with corneal tissue from a recently deceased person.

Descemet's membrane—Sheet of tissue that lies under the stroma and protects against infection and injuries.

Edema—Extreme amount of watery fluid that causes swelling of the affected tissue.

Endothelium—Extremely thin innermost layer of the cornea.

Epithelium—The layer of cells that cover the open surfaces of the body such as the skin and mucous membranes.

Hyaline—A clear substance that occurs in cell deterioration.

Stroma—Middle layer of the cornea, representing about 90% of the entire cornea.

Demographics

The diversity of corneal dystrophies diseases makes it difficult to provide specific demographic data. Some dystrophies appear in early childhood or even infancy, such as Reis-Bucklers' dystrophy. Others may not appear until middle age or beyond, as with Fuchs' dystrophy. Women are at greater risk for Fuchs' dystrophy, especially those over age 40. However, most corneal dystrophies present before age 20.

Signs and symptoms

The symptoms vary with the type of corneal dystrophy and the location of the site. Most experts categorize these diseases based on whether they are located on the anterior (outer) layer, stromal (middle) layer, or endothelial (inner) layer.

Anterior corneal dystrophies

The epithelium, or the "basement membrane," and the Bowman's layer together comprise the anterior, or outer part, of the cornea. Epithelial basement membrane dystrophy, also known as Cogan's map-dot-fingerprint dystrophy, is a disorder that causes errors in refractions of the eye and may also present with microscopic cysts. This disease results from excessive fluid (edema) and swelling of the basement membrane into the epithelium. Symptoms of this disease are map-like dots, opaque circles, or thin lines that are formed in a swirled pattern like fingerprints. Individuals with this disorder feel like they have something irritating in the eye and experience pain and light sensitivity (photophobia).

The tiny opaque collagen fibers that cause Reis-Bucklers' dystrophy create a linear or ring-like pattern. People with this disease have recurrent painful erosions of the cornea and may also suffer from severe visual impairment. Reis-Bucklers' is usually noticed in an infant or young child who suddenly has very red eyes. To the ophthalmologist, the cornea looks like frosted glass. This disorder may recur several times per year and disappear when affected individuals are in their 20s or 30s.

Stromal dystrophies

The primary dystrophies found in the stromal layer are granular dystrophy, lattice dystrophy, and macular dystrophy. Granular dystrophy is so named because of the small opaque areas caused by deposits of hyaline, a substance that accumulates as cells deteriorate. Lattice dystrophy is caused by deposits of amyloid, the same substance that accumulates in the brain in people with **Alzheimer disease**. Both granular dystrophy and lattice dystrophy have been identified in family members in Avellino, Italy, and these dystrophies are sometimes grouped together and called Avellino corneal dystrophy. Lattice and granular dystrophies can cause severe eye pain. With lattice dystrophy, by about age 40, an affected person's vision can be very obscured and a corneal transplant is required.

Endothelial dystrophies

Fuchs' dystrophy is the most common of the endothelial dystrophies and is inherited as an autosomal dominant trait. It is characterized by blurred vision, hypersensitivity to light (photophobia), and two to eight acute inflammatory attacks per year. It may also cause ulceration and erosion of the cornea. Fuchs' can cause deterioration of endothelial cells and result in corneal guttata, which are thickenings or leakages from the Descemet's membrane of the cornea. These guttata eventually cause edema (excessive fluid) to leak into the stromal or epithelial areas.

Posterior polymorphous dystrophy (PPD), an autosomal dominant disease, also causes edema, although it affects a larger area than Fuchs' dystrophy. It usually does not cause vision impairment.

Congenital hereditary endothelial dystrophy (CHED) comprises two types. The autosomal dominant

Gradual deterioration of the corneal tissue layers results in corneal dystrophy. As the tissue deteriorates, a gritty appearance such as that shown above, becomes apparent. *(Custom Medical Stock Photo, Inc.)*

form is CHED 1 and the recessive form is CHED 2. CHED 1 can occur in early childhood and may also cause hearing loss. The key symptoms of CHED 1 are sensitivity to light and excessive tearing. CHED 2 is present at birth and is more severe than CHED 1. In both CHED 1 and 2, the cornea presents with a milky haze or the appearance of ground glass.

Macular dystrophy is inherited as an autosomal recessive trait. It can present as early as age three and up to about age nine and is very debilitating. This disorder is caused by deposits of keratin sulfate (sulfur-containing fibrous proteins) and becomes increasingly painful. The child will have a feeling of something in the eye and also experience photophobia (sensitivity to light).

Diagnosis

Corneal dystrophy may be identified by an optometrist and diagnosed by an ophthalmologist. The findings determine the existence and type of corneal dystrophy. The presence, size, and shape of any opaque material in the eyes are considered.

The affected cornea of a person with lattice dystrophy will have a ground glass appearance, while granular deposits indicate granular dystrophy. The examination can also reveal the presence of amyloid deposits, which are typical of individuals with lattice dystrophy.

Treatment and management

Treatment depends on the severity of the disease. If the affected person is in acute pain, treatment with eye drops, antibiotics, and other solutions is necessary. Some doctors advise affected people with eye edema to use a hair dryer at arm's length to dry some of the edema. Soft contact lenses may also help. Individuals with increasingly severe vision problems may need a corneal transplant.

For other forms of corneal dystrophy, affected people may need artificial tears and other medications. Some individuals may need laser treatment, such as phototherapeutic keratectomy (PK), which is the removal of part of the corneal stroma, or they may need a corneal transplant.

Prognosis

With most forms of corneal dystrophy, the disease progresses as the affected person ages. The severity of the conditions varies and a particular form of the disease may

cause few or no problems or may also cause severe visual difficulties requiring surgery. Cases must be evaluated individually.

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National Association for Visually Handicapped. 22 West 21st Street, New York, NY 10010. (212) 889-3141. <http://www.navh.org>.

National Eye Institute. 31 Center Dr., Bldg. 31, Rm 6A32, MSC 2510, Bethesda, MD 20892-2510. (301) 496-5248. 2020@nei.nih.gov. <http://www.nei.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Christine Adamec

Cornelia de Lange syndrome

Definition

Cornelia de Lange syndrome is a congenital syndrome of unknown origin diagnosed on the basis of facial characteristics consisting of synophrys (eyebrows joined at the midline), long eyelashes, long philtrum (area between the upper nose and the lip), thin upper lip, and a downturned mouth. It is a multisystemic disease that most often affects the gastrointestinal tract and the heart. Patients also present with mental retardation as well as many skeletal system malformations. It is estimated that this syndrome affects one in 10,000 newborns.

Description

This syndrome was named after the physician who described the condition in Amsterdam in 1933. It is also known as Amsterdam Dwarf Syndrome of de Lange. In 1916, another physician named Brachmann first described a more severe form of this syndrome and therefore it is also known as Brachmann-de Lange syndrome. As of 2001, it is known that there are three distinct categories of this condition.

The most severe form of this condition is the Type I or "classic form". Patients with this form have a prenatal growth deficiency that is noticeable after birth. In addition, these patients are marked with a distinct face and moderate to profound mental retardation. These individuals often have major deformities in the gastrointestinal tract and heart which may lead to severe incapacity or death.

The mild form of this condition is known as the Type II form. This is characterized by similar facial features to that of Type I, however, they may not become apparent until later in life. Along with a less severe pre- and postnatal growth deficiency, major malformations are seen at a decreased rate or may be absent completely.

Type III Cornelia de Lange syndrome, also called phenocopy, includes patients who have phenotypic manifestations of the syndrome that are related to chromosomal aneuplodies or teratogenic factors.

Genetic profile

The syndrome is suspected to be genetic in origin but the mode of transmission is unknown. Most cases are sporadic and are thought to result from a new mutation (an abnormal sequence of the components that make a **gene**). There is also evidence that this may be transmitted in an autosomal dominant fashion, thus if only one parent is affected there exists a 50% chance of transmitting the abnormal gene to each child. A gene of chromosome 3 may be responsible for the syndrome.

Demographics

Cornelia de Lange syndrome appears to affect males and females in equal numbers. It is more common to see

affected females transmitting the trait, however, these women seem to transmit only the mild form to their offspring. It has also been noted that consanguineous relations, or relations within families, may result in an affected child. The recurrence risk has been estimated to be between two and six percent.

Signs and symptoms

Musculoskeletal abnormalities

- Microcephaly. Microcephaly is the term used to describe individuals with an abnormally small head. People with microcephaly have an accompanying small brain, resulting in mild to profound mental retardation.
- Micrognathia. This term is used when characterizing people with an abnormally small mandible or lower jaw bone.
- Nasal. Individuals with Cornelia de Lange syndrome often have a small nose. Anteversion, or turning, of the nostrils is also seen. A long philtrum (area between the nose and the upper lip) is also characteristic of a patient with Cornelia de Lange syndrome.
- Limb and digit malformations. Limb abnormalities sometimes include relatively short limbs. Limitations of elbow extension is often seen in mild forms. In addition, relative smallness of the hands and/or feet is almost always universal. Oligodactyly (presence of less than five digits on hand or feet), and clinodactyly or bending of the fifth finger and thumbs are also sometimes seen. Webbing of the toes (syndactyly) is also common in patients with Cornelia de Lange syndrome.
- Characteristic facial features. Facial features are possibly the most diagnostic of the physical signs. Patients look similar to each other with the bushy eyebrows joined at the midline, which is known as synophrys. Patients also have long eyelashes, a thin upper lip, and a downturned mouth. In mild cases, this classical appearance may not be present at birth and may take two or three years before becoming obvious. These individuals also have hypertrichosis, which is excessive facial (as well as body) hair.
- Other symptoms. Most patients are also of low birth weight, have a cleft palate, and a low-pitched growl or cry.

Gastrointestinal abnormalities

A number of gastrointestinal (GI) problems can manifest and are by far the most common system involved. Both the upper and lower GI tract can be involved.

- Gastroesophageal reflux. This is caused when acid from the stomach refluxes back into the esophagus. This can lead to severe heartburn and, if left untreated, can cause damage to the esophagus (reflux esophagitis) due to repeated irritations. Gastroesophageal reflux can also cause symptoms of pulmonary congestion and irritation due to chemical pneumonitis (inflammation of the lung).
- Barrett's esophagus. Barrett's esophagus is a change from the normal tissue type of the lower esophagus to a different type. This is normally a complication on gastroesophageal reflux and is significant because it may develop into an adenocarcinoma (carcinoma of glandular tissue).
- Esophageal stenosis. A narrowing of the esophagus which may decrease esophageal motility and make feeding difficult.
- Gastric ulcers. The majority of ulcers of the stomach are caused by bacteria. Ulcers of this nature may lead to abdominal discomfort.
- **Pyloric stenosis**. A narrowing of the pyloric canal that leads from the stomach to the duodenum. This may result in vomiting and diarrhea complicated by electrolyte imbalances.
- Intestinal malrotation. This is a failure during fetal development of normal rotation of the small intestine. This can cause a volvulus, a twisting of the intestine back on itself, cutting-off blood supply to the tissue or possibly an intestinal obstruction.
- **Meckel diverticulum**. In this condition, there are tiny pouches that protrude in the small intestine. Sometimes ulceration develops and bleeding occurs.

Cardiac abnormalities

Heart problems are not uncommon in patients with Cornelia de Lange syndrome.

- Ventricular septal defect. In this condition the septum of the ventricles (wall between the lower chambers of the heart) is not fully closed. This results in a murmur and can possibly lead to congestive heart failure. Other complications may include infective endocarditis, which is an infection of the endothelium, the tissue that lines the heart.
- Atrial septal defect. This is a defect of the septum between the upper chambers of the heart. It is caused by the persistence of the foramen ovale which is a hole normally present in the fetus that closes at birth. Individuals with this condition may also have a heart murmur.
- Symptoms are normally not present in patients with atrial septal defects but they are at an increased risk of infective endocarditis.

- **Patent ductus arteriosus**. This is a failure of the ductus arteriosus, a blood vessel between the pulmonary artery and the aorta found only in the fetus, to close. Normally, there are symptoms but severe cases may require surgery to close.
- Pulmonary valve stenosis. In this condition, the valve that allows blood to go from the right ventricle to the lungs becomes narrowed. This may result in right-sided heart enlargement and heart failure.
- Tetralogy of Fallot. This is a condition consisting of pulmonary stenosis, ventricular septal defect, enlarged right ventricle, and a displaced aorta. This condition results in a decrease in oxygenated blood that is pumped to the body. It can normally be corrected by surgery.

Growth and developmental deficiency

Most people afflicted with Cornelia de Lange syndrome have both prenatal and postnatal growth deficiencies as well as a developmental delay. This may be due to endocrine system involvement concerning a growth hormone delivery problem. Most patients have a characteristically short stature, but often have a pubertal growth spurt at a comparable age to normal individuals.

Developmental delays are numerous and are found in most patients with Cornelia de Lange syndrome. Some of the delays include walking alone, speaking, toilet training, and dressing. In some instances these patients never reach these milestones. Other developmental delays include IQ, which is within the mild to moderate range for mental retardation and averages 53.

Disorders of ears and eyes

Many patients with Cornelia de Lange syndrome often have some form of hearing loss. Cases may range from mild to severe, and may affect either one or both ears. This loss can be attributed to a lack of prenatal development of some of the important bony structures associated with the inner ear. In addition, development failure of important neural elements play a role in this hearing loss.

A significant number of Cornelia de Lange syndrome patients have eye and/or vision problems including:

- Myopia. Nearsightedness or shortsightedness is often seen in children diagnosed with Cornelia de Lange syndrome.
- Nystagmus. This is the term used to describe the rhythmical oscillations of the eyes slowly to one side followed by a rapid reflex movement in the opposite direction. It is usually horizontal, although rotatory or vertical nystagmus may also occur.
- Ptosis. Ptosis is the medical term used to characterize patients having a drooping eyelid(s). This may result from lesions either in the brainstem or in the nerves supplying the muscles that raise the eyelid.
- Nasolacrimal duct fistula. The lacrimal gland secretes tears to keep the eyeball moist and protected. In a nasolacrimal duct fistula the tears are not drained from the eyeball and therefore the patient may develop chronic tearing and discharge from the eyes.

Other symptoms

Other malformations include undescended testicles, which can cause fertility problems. Diaphragmatic hernia is another complication that may lead to GI difficulties. Patients may also have a cleft palate and a low-pitched growl or cry.

Diagnosis

Cornelia de Lange syndrome has no set criteria that can indicate with absolute certainty whether or not a child is afflicted. This is due in part to a lack of specific biochemical markers postnatally that would lead a clinician to a definitive diagnosis. However, diagnosis is made subjectively from the characteristic symptoms that are present in this condition including the ones listed above. Perhaps the most diagnostic tool is the distinguishing face that a patient has, combined with facial hypertrichosis.

Prenatal diagnosis is possible through the use of ultrasound. The association of intrauterine growth retardation, oligodactyly, an absent ulna, underdevelopment of hands, diaphragmatic hernia, and cardiac defects lead to the differential diagnosis. When uncertain, the presence of long eyelashes or unusually long hair on the back restrict the diagnosis to Cornelia de Lange syndrome.

Researchers have also found that maternal serum samples collected from women who gave birth to a child with Cornelia de Lange syndrome revealed low levels of a pregnancy associated plasma protein-A (PAPP-A) during the second trimester. In addition, it has been noted that an amniotic molecule (5-OH-indole-3-acetic acid), and a fetal serum protein (galactose-1-phosphate-uridyltrasferase) were increased in afflicted individuals.

Treatment and management

The treatment and management of patients with Cornelia de Lange syndrome is strictly symptomatic.

This means that treatment is prescribed according to presenting symptoms.

Musculoskeletal concerns

For patients with limb and digit malformations a variety of prosthesis are advised if necessary. Physical and occupational therapy may also be needed. Surgery may be necessary to correct more severe deformities.

Gastrointestinal treatment

Gastroesophageal reflux disease (GERD) can be treated with special diets and a number of different drugs that either block acid secretion from the stomach or neutralize acid once it is produced. Drugs may include antacids, histamine receptor blockers, and proton pump inhibitors. If these treatments prove unsuccessful, surgery my be performed to eliminate the possibility of further complications such as Barrett's esophagus or esophageal stenosis.

Patients with Cornelia de Lange syndrome should have endoscopic evaluation with biopsies for Barrett's esophagus. If this occurs, treatment will include the aforementioned drugs to reduce stomach acid and removal of the precancerous tissue may be indicated. Surgery to shorten the esophagus may also be performed.

Esophageal stenosis treatment may include a procedure done in order to dilate the esophagus. Some patients may require surgery to implant a stent or to replace part of the esophagus.

Gastric ulcers are often treated by the same means used to treat GERD. In addition, antibiotics are used in order to eliminate any bacteria that may be the cause of the ulcer. Sucralfate may be used to form a barrier over the ulcer that protects it from stomach acid allowing it to heal.

Patients with pyloric stenosis normally require surgery in order to widen the canal leading from the stomach to the duodenum. In addition, those with intestinal malrotation may require surgery depending on the severity of the condition. Surgery may also be required for patients with Meckel diverticulum if bleeding is a problem.

Cardiovascular treatment

In mild cases of cardiovascular involvement, no treatment plan is initiated other than to monitor the dysfunctions. Some of the septal defects may be asymptomatic and heal on their own. Since most of these abnormalities can lead to infective endocarditis, patients should be given antibiotics before undergoing dental procedures or surgeries. Most often penicillin or amoxicillin are used.

For patients who develop congestive heart failure, a regiment of drugs known as beta blockers may be useful to slow down the heart. Other drugs that may be used are diuretics to prevent fluid retention or ACE inhibitors.

For more serious cardiac involvement surgery is recommended. Surgery for tetralogy of Fallot involves widening the pulmonary valve and repairing the ventricular septal defect. This surgery is normally performed on patients between the ages of eight months and three years. Ventricular septal defects can be repaired usually with a synthetic patch. Atrial septal defects are normally performed by catherization by placing a device between the atria in the septum. Patent ductus arteriosus correction is done by either ligating the vessel or cutting it off.

Hearing and visual concerns

Patients diagnosed with Cornelia de Lange syndrome should be examined for hearing loss as soon as possible due to the possibility of speech delay that may

KEY TERMS

Chromosomal aneuplodies—A condition in which the chromosomal number is either increased or decreased.

Clinodactyly—An abnormal inward curving of the fingers or toes.

Consanguineous—Sharing a common bloodline or ancestor.

Fistula—An abnormal passage or communication between two different organs or surfaces.

Hypertrichosis—Growth of hair in excess of the normal. Also called hirsutism.

Infective endocarditis—An infection of the endothelium, the tissue lining the walls of the heart.

Oligodactyly—The absence of one or more fingers or toes.

Syndactyly—Webbing or fusion between the fingers or toes.

Synophrys—A feature in which the eyebrows join in the middle. Also called blepharophimosis.

Teratogenic factor—Any factor that can produce congenital abnormalities.

be experienced because of this loss. Patients should be fitted with hearing aids and may be considered for pharyngeal-esophageal tubes.

It is also important to identify vision problems early. Glasses may be necessary for nearsightedness. Children should be seen by an opthamologist in order to assess limitations and to develop a treatment plan.

Other issues

Since development of speech is often delayed, people affected with Cornelia de Lange syndrome should be seen by a speech pathologist at an early age. Alternative communication strategies, such as sign language, may be employed depending on the level of speech development.

Children and family members may also benefit from therapy available from a number of organizations. Patients may qualify for health related support services from a variety of national support services for retarded persons.

Prognosis

Patients with Cornelia de Lange syndrome can live well into adulthood, however, it is typical for most to have a shortened lifespan. In 1976, a nationwide survey in Denmark revealed the oldest patient was found to be 49 years old.

A patient's prognosis can be improved by early diagnosis and intervention. These two factors can influence not only the patients life expectancy, but also their quality of life and those lives of the family and caregivers.

Resources

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ORGANIZATIONS

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

Cornelia de Lange Syndrome Foundation, Inc. 302 West Main St., Suite 100, Avon, CT 06001. (860) 676-8166 (800) 223-8355. Fax: (860) 676-8337.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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WebMD. <http://www.webmd.com>.

Laith F. Gulli, MD
Robert Ramirez, BS

Costello syndrome

Definition

Newborn feeding problems, poor growth, loose, wrinkled skin, and mental retardation are some of the recognizable features of Costello syndrome. Although the genetic basis is unknown, the unusual skin features have given an important clue as to the cause of the disorder.

Description

The first sign of Costello syndrome may be seen even before birth. Many mothers carrying these babies have polyhydramnios (an excess of amniotic fluid in the womb). This may be due to the fact that the baby has poor swallowing ability, even in the womb. Many of these babies are large at birth, especially with respect to their weight. Their head size is usually larger too. Most significant, all of these babies begin life with severe feeding problems. They do not grow and thrive as most babies do. As this continues, they lose weight and become quite ill. Their height also tapers off. This poor growth continues until about two years of age. Then, for reasons unknown, their growth, especially weight gain, becomes more normal. However, these children continue to grow more slowly in height, and remain short throughout life. Most adults with Costello syndrome are approximately 4.5 ft (1.5 m) tall. X-ray studies done at different ages show that bone growth is delayed. The delay in normal bone growth leads to reduced height.

Some interesting features of the face and loose, soft skin add to the clinical picture. Even as babies, individuals with Costello syndrome have a slight downward slant of their eyes, full cheeks, and thick lips. The neck is short, and they have an upturned nose. The ears are low set (below the level of the nose) with large, fleshy ear lobes. These features seem to coarsen and become more noticeable over time. However, the signature feature of Costello syndrome is the soft, deeply wrinkled skin, especially on the hands and feet. This is evident at birth and becomes even more striking in the first few months of life. All individuals with Costello syndrome have these deep creases and looseness of the skin. Some physicians have described the distinct, deep creases in the skin as resembling “bath tub hands,” i.e. similar to the puffiness seen after soaking one’s hands in water for awhile.

Other features of Costello syndrome include skin markings, sparse, curly hair, and a hoarse voice. Individuals with Costello syndrome have unusual skin growths called papillomatous papules, which are skin-colored, raised bumps (not warts). These papules are found on the skin inside the nose and mouth, on the tongue, and around the anus. The papules form in late childhood or early teenage years. Most of these growths are benign (non-cancerous) and rarely become malignant (cancerous). Other skin markings may include dark colored moles on the palms of the hands and on the bottom of the feet; brownish colored skin marks (birthmarks) found almost anywhere on the body; and small, red marks which are broken blood vessels on the surface of their skin.

Most individuals with Costello syndrome also have sparse, curly hair. The hair turns gray in color at a much earlier age than expected (sometimes even in teenage years). Along with the loose, wrinkled skin, the graying of the hair makes them look much older than their age. The last feature of note is their voice, many times described as being low and hoarse. It has been suggested that the hoarse voice may possibly be due to weakness in the tissues or muscles of the larynx.

Cardiovascular problems are common in children with Costello sydrome. Among the **congenital heart defects** seen are atrial or ventricular septal defects, **bicuspid aortic valve**, **patent ductus arteriosus**, and mitral valve prolaspe. More than half of the reported cases of Costello sydrome included heart rhythm disturbances and abnormalities in the structure and functions of the heart muscle (hypertrophic cardiomyopathy).

Genetic profile

As of 2001, the genetic basis of Costello syndrome is unknown. There have been two instances where siblings (brother and sister) each had Costello syndrome. The sydrome has also occurred in a few families where the parents were said to be closely related (i.e., may have shared the same altered **gene** within the family). For these reasons, the possible involvement of an autosomal recessive gene in Costello syndrome was raised. An autosomal recessive condition is caused by a change in both genes of a pair.

As more individuals with Costello syndrome were described, the evidence began to suggest autosomal dominant **inheritance**. This means only one altered copy of a gene pair is needed to cause the disorder. The cases of Costello syndrome that occur for the first time in a family are probably due to a new, sporadic (non-inherited) **gene mutation**. To explain the two families with more than one child with Costello syndrome, the concept of germ line mosaicism was proposed.

Germ line mosaicism occurs when one parent carries an altered gene mutation that affects his or her germ line cells (either the egg or sperm cells) only. The gene mutation does not affect the somatic (body) cells. Therefore, the parent does not express the disease and DNA testing

KEY TERMS

Arrhythmia—Abnormal heart rhythm, examples are a slow, fast, or irregular heart rate.

Elastin—A protein that gives skin the ability to stretch and then return to normal.

Ganglioneuroblastoma—A tumor of the nerve fibers and ganglion cells.

Germ line mosaicism—A rare event that occurs when one parent carries an altered gene mutation that affects his or her germ line cells (either the egg or sperm cells) but is not found in the somatic (body) cells.

Larynx—The voice box, or organ that contains the vocal cords.

Papillomatous papules—Skin-colored, raised bumps (not warts) found on the skin. Most of these growths are benign (non-cancerous) and rarely become malignant (cancerous).

Polyhydramnios—A condition in which there is too much fluid around the fetus in the amniotic sac.

Rhabdomyosarcoma—A malignant tumor of the skeletal muscle.

does not show that the parent carries an altered gene. However, parents with germ line mosaicism can have more than one child with a disorder (like Costello syndrome) since the syndrome occurs whenever an egg or sperm carrying the altered gene mutation is passed on. Germ line mosaicism occurs very rarely. However, it has been seen in other autosomal dominant conditions, such as **osteogenesis imperfecta** (brittle bone disease). Based on the available evidence, Costello syndrome is probably an autosomal dominant condition. In some families, germ line mosaicism explains the pattern of expression of the condition.

Most individuals with Costello syndrome have undergone extensive testing to look for a cause for their growth and developmental problems. For the most part these tests have been normal. The underlying problem appears to be complex. However, some researchers had the idea to look more closely at the makeup of the skin cells for clues to the disorder.

Stretchable tissues like the skin require not only strength but also the ability, once stretched, to return to their original form. Human skin is made up of a network of fibers that give the skin its flexibility. The fibers themselves are made out of different proteins. One such protein is called elastin. Elastin acts like a rubber band in the skin. It can be stretched and then returns to its original form. Within our skin cells, the elastin protein is randomly twisted and tied to form elastin fibers. A study of the skin cells of individuals with Costello syndrome shows that the elastin fibers do not appear to be formed in the normal way. The skin cells seem to stretch but do not have the ability to snap back, as do normal skin cells. Thus, the skin has a loose and wrinkled appearance. Specifically, a protein called the elastin binding protein seems to play a role in forming the elastin fibers. In Costello syndrome, this protein is abnormal causing the elastin fibers themselves to become loose and disrupted.

The defect in the elastin building pathway explains many of the clinical features of Costello syndrome, especially the loose and wrinkled skin. Elastin fibers make up tissues of the heart, the larynx, even the developing skeleton. Therefore, the heart disease, the hoarse voice, even the short height may be explained by abnormal formation of the elastin fibers.

Demographics

In 1971, and later in 1977, Dr. J. Costello first described a syndrome of mental and growth delays, and distinct features of the face and skin that bear his name. After the initial description, there were no further reports of individuals with Costello syndrome until 1991. It was then that the term Costello syndrome was used to describe the features seen in a Canadian child. Further cases from several countries have since been reported. In all, at least 40 individuals with Costello syndrome have been described in medical literature. The condition may be more common than previously thought, and may be under diagnosed. It affects both males and females equally, and most likely occurs in every racial and ethnic group.

Signs and symptoms

All individuals with Costello syndrome have fairly significant mental retardation. This impairment leads to early delays in walking and talking. They are usually a few years behind other children their age. These learning problems continue as they get older, and require a special education environment. IQ testing in some individuals with Costello syndrome has shown a range from mild to moderate retardation (IQ from 30 to 68). Although they have special needs, their outgoing and friendly personality is an asset, and helps them make the most of their abilities.

Diagnosis

The pattern of overgrowth in the womb, poor growth after birth, and short height is typical of individuals with

Costello syndrome. Other clinical features, especially the loose, wrinkled skin and graying, curly hair give them an aged appearance that is quite distinct. The skin papules found in the nose, mouth, and on the anus add to the picture. Taking these features together, the diagnosis can be made.

Treatment and management

Heart disease is seen in almost half of the individuals with Costello syndrome. The heart problems are sometimes found at birth. The heart problems include holes in the muscle wall of the heart; abnormal thickening of the walls of the heart; and an abnormal heart beat or arrhythmia. An echocardiogram (ultrasound of the heart) is usually done early in life to assess heart function. Heart function is also closely monitored as these individuals get older.

At least eight individuals (of the 40 or so now described) with Costello syndrome have developed rare types of **cancer**. The cancers have occurred early in life, and a few cases have occurred in infancy. The tumors seen include two cases of ganglioneuroblastoma, a tumor of the nerve fibers; three cases of rhabdomyosarcoma, a tumor of the skeletal muscle; and two cases of bladder cancer in teenagers, a cancer usually seen in the elderly.

Prognosis

The severe problems with feeding and growth that characterize Costello syndrome can be life-threatening. Most of these infants need to be fed with a feeding tube in order to survive. Complications of heart disease are another cause for concern, even early in life. For most individuals, however, the heart problems are not severe, and usually can be successfully treated without heart surgery. Unfortunately, some individuals with Costello syndrome experienced heart failure and sudden death. Lastly, there may be an increased risk for developing cancer. Since some of these individuals have died from complications of their cancer, increased screening may be important to detect cancer at an early stage.

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Kevin M. Sweet, MS, CGC

CPT II deficiency *see* **Carnitine palmitoyl transferase deficiency**

Crane-Heise syndrome

Definition

Crane-Heise syndrome is a lethal genetic disorder first defined in 1981. Some of the features of Crane-Heise syndrome are similar to those of another genetic disorder called aminopterin syndrome sine aminopterin (or pseudoaminopterin syndrome), indicating that the two conditions may be part of a spectrum of symptoms.

Description

Aminopterin syndrome is an established disorder resulting from the use of aminopterin as an abortifacient. Surviving infants who had been exposed to this chemical had severe developmental abnormalities, especially those of the skull. Crane-Heise is distinct from aminopterin syndrome in that the mothers of infants with Crane-Heise syndrome were not exposed to aminopterin.

Genetic profile

There are very few documented cases of Crane-Heise syndrome, and therefore, little is known about the genetic basis of the disorder. As of 2001, no specific chromosome or **gene** location has been identified.

Since Crane-Heise syndrome has affected more than one sibling in a family, and has been seen in both males and females, it is most likely transmitted through autosomal recessive **inheritance**. This means that two copies of the abnormal gene would have to be inherited, one from each parent, in order for the disorder to occur.

Demographics

Males and females are at equal risk for inheriting Crane-Heise syndrome since it is assumed to be an auto-

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

somal trait, meaning it is not inherited on one of the sex-determining **chromosomes**. No one ethnic group has been shown to be at higher risk, primarily due to the few number of reported cases. Of the cases reported, there tends to be a frequent reoccurrence of the disease with each pregnancy.

Signs and symptoms

Many distinct characteristics are seen in infants with Crane-Heise syndrome. Some of these include:

- Large head with a relatively small face
- Depressed nose with nasal openings turned forward
- Underdeveloped jaw
- A narrow nose bridge with eyes close together
- Low-set ears that are turned to the back
- Short neck
- Partially fused fingers or toes
- **Clubfoot**

The most definitive features of Crane-Heise syndrome and aminopterin syndrome are the cranial and bone abnormalities. Infants born with these syndromes typically have absent or underdeveloped brains (**anencephaly**), underdeveloped shoulder blades, and absent collarbones and vertebrae.

Diagnosis

Since the signs of Crane-Heise syndrome are nearly identical to those observed in infants with aminopterin syndrome, it is important to identify whether or not the mother was exposed to aminopterin for differential diagnosis. Some fetuses have been diagnosed with Crane-Heise syndrome in the uterus via ultrasonography, however most diagnoses are based on physical examination at the time of birth.

Treatment and management

As of 2000, no treatment has been developed. Further research to better understand the cause and genetic basis of this disorder is necessary.

Prognosis

Crane-Heise syndrome is a lethal disorder and infants are usually stillborn or survive only a few days after birth. Malformations of the brain and vertebrae are usually severe and cannot be corrected surgically.

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Sonya Kunkle
Stacey L. Blachford

Craniofrontonasal dysplasia *see* **Otopalatodigital syndrome**

Craniostenosis *see* **Craniosynostosis**

Craniosynostosis

Definition

Craniosynostosis is a congenital abnormality of the central nervous system that involves the premature closing of one or more of the fibrous joints between the bones of the skull (cranial sutures).

Description

Craniosynostosis is a birth defect that affects the shape of the skull. Individuals born with craniosynostosis have abnormally shaped heads and a prominent bony ridge over the affected suture or sutures. All affected individuals also are likely to experience water on the brain (**hydrocephalus**) that can cause enlargement of the head and increased pressure inside the skull. Developmental delay is commonly experienced by those individuals affected by craniosynostosis.

There are two major classifications of craniosynostosis: primary and secondary. There are multiple causes

of primary craniosynostosis, which involves abnormal cranial suture development. The premature closure of one or more of the sutures causes the skull bones to grow parallel to the affected suture but not perpendicular to it. At other sutures there may be too much growth. The disrupted growth patterns cause a misshapen skull. The cause of secondary craniosynostosis is failure of the brain to grow and expand. This results in uniform premature suture closure, so that the head is symmetric and abnormally small (microcephalic).

The human skull consists of several bony plates separated by a narrow gap that contains stem cells. These fibrous joints are referred to as cranial sutures. There are six cranial sutures: the sagittal, which runs from front to back across the top of the head; the two coronal sutures, which run across the skull parallel to and just above the hairline; the metopic, which runs from front to back in front of the sagittal suture; and the two lambdoid sutures, which run side to side across the back of the head. There are seven types of primary craniosynostosis divided by the cranial suture or sutures that are affected: sagittal, bicoronal (both coronal sutures), unicoronal (one coronal suture), coronal and sagittal, metopic, lambdoid and sagittal, and total, in which all the cranial sutures are affected. Approximately 40% of all cases of craniosynostosis are sagittal, 20% are bicoronal, 15% are unicoronal, 10% are coronal and sagittal, 4% are metopic, 1% are lambdoid and sagittal, and 10% are total.

Genetic profile

Craniosynostosis does not have a single genetic cause, but it has been demonstrated to have a genetic component in that it is sometimes passed from one generation to another. It has been associated with over 150 different genetic syndromes. Genetic **inheritance** of craniosynostosis is not sex-linked (it is autosomal), and has been tied to both dominant and recessive traits. The overall occurrence rates are equivalent between males and females, but sagittal craniosynostosis is seen four times as often in males as in females, while coronal craniosynostosis is observed twice as often in females as in males.

As of 1997, 64 distinct mutations in six different genes have been linked to craniosynostosis. Three of these genes, at chromosome locations 8p11, 10q26, and 4p16, are related to fibroblast growth factor receptors (FGFRs), which are molecules that control cell growth. Other implicated genes are the TWIST **gene** (7p21), the MSX2 gene (5q34-35), and the FBN1 gene (15q21.1).

Not all instances of craniosynostosis appear to have a genetic origin. The most common cause of non-genetic craniosynostosis is constraint of the fetal head during pregnancy. This is believed to account for between 50 and 60% of all cases of craniosynostosis.

Known genetic syndromes account for another 10 to 20% of the cases of craniosynostosis. These syndromes include Muenke syndrome, **Apert syndrome**, **Pfeiffer syndrome**, **Carpenter syndrome**, and **Crouzon syndrome**, among others.

Demographics

Craniosynostosis has an incidence of approximately one in every 2,000 live births. Genetic-based craniosynostosis is most commonly a dominant trait, but in some cases has also been shown to be recessive. Therefore, while it is more likely to occur in children with a family history of craniosynostosis, it may not occur in the children of such families and it may also occur in children with no family history of the disorder. Non-genetic craniosynostosis has a higher occurrence among the children of malnourished or drug-abusing mothers. It is also more likely to occur in the children of teenage mothers because of the lack of development of an appropriately sized uterus for fetal growth in many of these cases.

Signs and symptoms

The most obvious symptom of craniosynostosis is an abnormally shaped head that is not the result of the birth process. Craniosynostosis may be confirmed by the presence of a bony ridge over the affected cranial suture. Associated symptoms include unusual facial features such as wide-set, down-slanting, or protruding eyes and a prominent jaw; visual impairment; hearing loss; breathing problems; water on the brain (hydrocephalus); and developmental delay.

Each type of craniosynostosis has different physically observable symptoms and results in a different head shape. Sagittal craniosynostosis is characterized by a long and narrow skull (scaphocephaly). This is referred to as an increase in the A-P, or anterior-to-posterior, diameter. Thus, looking down on the top of the skull, the diameter of the head is greater than normal in the front-to-back direction. Individuals born with sagittal craniosynostosis have broad foreheads and a larger than normal back of the head. The so-called soft spot found just beyond the hairline in a normal baby (the anterior fontanelle) is missing or very small in a baby affected with sagittal craniosynostosis. The result of neurological testing is generally normal for individuals with sagittal craniosynostosis.

Bicoronal craniosynostosis is characterized by a wide and short skull (brachycephaly) or by a cloverleaf-shaped skull. This is referred to as a decrease in the A-

KEY TERMS

Acrocephalopolysyndactyly syndromes—A collection of genetic disorders characterized by cone shaped abnormality of the skull and partial fusing of adjacent fingers or toes.

Acrocephaly—An abnormal cone shape of the head.

Anterior fontanelle—The soft-spot on the skull of an infant that is located in the center of the head just behind the hairline.

Brachycephaly—An abnormal thickening and widening of the skull.

Congenital—Refers to a disorder which is present at birth.

Cranial suture—Any one of the seven fibrous joints between the bones of the skull.

Frontal plagiocephaly—An abnormal condition of the skull in which the front is more developed on one side than it is on the other side.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Microcephalic—Having an abnormally small head.

Primary craniosynostosis—Abnormal closure of the cranial sutures caused by an abnormality in the sutures themselves.

Proptosis—Bulging eyeballs.

Scaphocephaly—An abnormally long and narrow skull.

Secondary craniosynostosis—Abnormal closure of the cranial sutures caused by a failure of the brain to grow and expand.

Trigonocephaly—An abnormal development of the skull characterized by a triangular shaped forehead.

P diameter. Individuals affected with bicoronal craniosynostosis have poorly formed eye sockets and foreheads. This causes a lower than normal sized eye-socket which can cause complications of vision. These complications include damage to the optical nerve which can cause a loss of visual clarity; bulging eyeballs (a condition called proptosis) that usually results in damage to the cornea; widely spaced eyes; and, a narrowing of the sinuses and tear ducts that can cause inflammation of the mucous membranes that line the exposed portion of the eyeball (conjunctivitis). Bicoronal craniosynostosis can be further complicated by water on the brain (hydrocephalus) and increased intracranial pressure. Most individuals affected with bicoronal craniosynostosis also have an abnormally high and arched palate that can cause dental problems and protrusion of the lower jaw. Bicoronal craniosynostosis is associated with the Acrocephalosyndactyly syndromes (genetic syndromes that involve abnormalities of the head and webbed fingers or toes), which include Apert syndrome, Apert-Crouzon syndrome, Chotzen syndrome, and Pfeiffer syndrome.

Unicoronal craniosynostosis is characterized by a skull that is more developed in the front on one side than it is on the other side (frontal plagiocephaly). This leads to a distinct asymmetry between the sides of the face, a flattening of the forehead on the side affected by the premature suture closure, and a misalignment of the eyes such that the eye on the affected side is higher than the eye on the unaffected side.

Coronal and sagittal craniosynostosis is characterized by a cone-shaped head (acrocephaly). The front soft-spot (the anterior fontanelle) is generally much larger than normal and it may never close without surgical intervention. Individuals affected with coronal and sagittal craniosynostosis may have higher than normal intracranial pressure. Pfeiffer syndrome is closely associated with coronal and sagittal craniosynostosis.

Total craniosynostosis is characterized by a normally shaped but small skull (microcephaly). Individuals affected with total craniosynostosis have higher than normal intracranial pressures and they are the most likely of all craniosynostosis affected individuals to suffer from developmental delay.

Metopic craniosynostosis is characterized by a triangular shaped forehead (trigonocephaly) and thickened bones in the forehead and narrowly spaced eyes. Individuals affected with metopic craniosynostosis tend to have developmental abnormalities associated with processes that are known to be controlled by the front of the brain (the forebrain). Lambdoid and sagittal craniosynostosis is the most rare type of craniosynostosis. It is characterized by a flattening of the back of the skull (the occipital bone) and a bulging of the front of the skull (the frontal bone). This condition may occur symmetrically or asymmetrically.

Diagnosis

Prenatal, transabdominal, or traditional ultrasound is generally used to assess fetal skull development in the second and third trimesters of pregnancy. As of 2000, the

resolution of such images is not always clear enough for a confident diagnosis of craniosynostosis. A transvaginal ultrasonic test to detect skull abnormalities in fetuses has been conducted in Japan and it offers much higher image clarity, allowing for the direct observation of cranial suture development as early as the second trimester, particularly of the sagittal and coronal sutures. Bicoronal and unicoronal craniosynostosis associated with one of the acrocephalosyndactyly syndromes may be detected via two different genetic tests now available that are able to identify the underlying mutations in the FGFR or TWIST genes. The sensitivity of this test is very high for certain genetic syndromes associated with coronal craniosynostosis: 100% for Muenke syndrome and 98% for Apert syndrome.

Almost all cases of craniosynostosis are evident at birth; however, the cranial sutures are not fully closed at this time so instances of craniosynostosis have been diagnosed later in infancy as well. Skull x rays and/or a CT scan may also be used after birth to diagnose craniosynostosis.

Treatment and management

Since craniosynostosis is associated with other conditions and may require multiple treatments of the skull, face, eyes, and ears, a multidisciplinary team of doctors and specialists is often required. The skull abnormalities of craniosynostosis should be surgically corrected within the first year of life. In the first year of life, changing the elevation and contours of the skull bones is much easier and new bone growth and reshaping occur rapidly. Also, at this point, the facial features are still highly undeveloped, so significant improvement in appearance can be achieved. Multiple surgeries may be required over the patient's lifetime, depending on the circumstances of the case. Follow-up support by pediatric, psychological, neurological, surgical and genetic specialists may be necessary.

In the types of craniosynostosis that involve the eyes, consultation with an ophthalmologist is recommended and eye surgery may be necessary. Speech and hearing therapy may also be needed when the ears and the frontal lobe have been affected. In the case of bicoronal craniosynostosis where the palate is severely malformed, dental consultation may also be required. In the most severe cases of coronal craniosynostosis, it will be necessary to address feeding and respiratory problems that are associated with the abnormally formed palate and sinuses.

Families with a history of craniosynostosis can participate in **genetic counseling** in order to learn whether **genetic testing** can identify the likelihood that their children might be affected.

Prognosis

In all but the most severe and inoperable cases of craniosynostosis, it is possible that considerable improvement in physical appearance can be achieved via surgery. Depending on the neurological damage resulting from certain types of craniosynostosis versus the rapidity of treatment, certain affected individuals may suffer developmental disabilities ranging from the extremely mild to very severe. Most individuals with craniosynostosis that involves the coronal sutures will continue to have vision problems throughout life. These problems vary in severity and many are now amenable to fully corrective treatments.

Resources

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ORGANIZATIONS

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

Craniosynostosis and Parents Support. 2965-A Quarters, Quantico, VA 22134. (877) 686-CAPS or (703) 445-1078. <http://www.caps2000.org/>.

WEBSITES

Craniosupport. <http://www.craniosupport.com/>.

Pediatric Database (PEDBASE) Homepage. <http://www.icondata.com/health/pedbase/files/CRANIOSY.HTM>.

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Paul A. Johnson

Creutzfeldt-Jakob disease *see* **Prion diseases**

Cri du chat syndrome

Definition

Cri du chat syndrome occurs when a piece of chromosomal material is missing from a particular region on chromosome 5. Individuals with this syndrome have unusual facial features, poor muscle tone (hypotonia), small head size (microcephaly), and mental retardation.

KEY TERMS

Aminocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Centromere—The centromere is the constricted region of a chromosome. It performs certain functions during cell division.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Congenital—Refers to a disorder which is present at birth.

Deletion—The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

Hypotonia—Reduced or diminished muscle tone.

Karyotyping—A laboratory procedure in which chromosomes are separated from cells, stained and arranged so that their structure can be studied under the microscope.

Microcephaly—An abnormally small head.

A classic feature of the syndrome is the cat-like cry made by infants with this disorder.

Description

Dr. Jerome Lejeune first described cri du chat syndrome in 1963. The syndrome is named for the cat-like cry made by infants with this genetic disorder. *Cri du chat* means "cry of the cat" in French. This unusual cry is caused by abnormal development of the larynx (organ in the throat responsible for voice production). Cri du chat syndrome is also called "5p minus syndrome" because it is caused by a deletion, or removal, of genetic material from chromosome 5. The deletion that causes cri du chat syndrome occurs on the short or "p" arm of chromosome 5. This deleted genetic material is vital for normal development. Absence of this material results in the features associated with cri du chat syndrome.

A high-pitched mewing cry during infancy is a classic feature of cri du chat. Infants with cri du chat also typically have low birth weight, slow growth, a small head (microcephaly) and poor muscle tone (hypotonia). Infants with cri du chat may have **congenital heart defects**. Individuals with cri du chat syndrome have language difficulties, delayed motor skill development, and mental retardation. Behavioral problems may also develop as the child matures.

Genetic profile

Cri du chat is the result of a chromosome abnormality. Human beings have 46 **chromosomes** in the cells of the their body. Chromosomes contain genes, which regulate the function and development of the body. An individual's chromosomes are inherited from their parents, 23 chromosomes from the egg and 23 chromosomes from the sperm. The 46 chromosomes in the human body are divided into pairs based on their physical characteristics. Chromosomes can only be seen when viewed under a microscope and appear identical because they contain the same genes.

Most chromosomes have a constriction near the center called the centromere. The centromere separates the chromosome into long and short arms. The short arm of a chromosome is called the "p arm". The long arm of a chromosome is called the "q arm".

Individuals should have two copies of chromosome 5. Cri du chat is caused when a piece of material is deleted, or erased, from the "p" arm of one chromosome 5. The piece of chromosomal material deleted contains many genes necessary for normal development. When these genes are missing, the larynx, brain, and other parts of the body do not develop as expected. This is what causes the symptoms associated with cri du chat.

In 90% of patients with cri du chat syndrome, the deletion is sporadic. This means that it happens randomly and is not hereditary. If a child has cri du chat due to a sporadic deletion, the chance the parents could have another child with cri du chat is 1%. In approximately 10% of patients with cri du chat, there is a hereditary chromosomal rearrangement that causes the deletion. If a

parent has this rearrangement, the risk for them to have a child with cri du chat is greater than 1%.

Demographics

It has been estimated that cri du chat syndrome occurs in one of every 50,000 live births. According to the 5p minus Society, approximately 50-60 children are born with cri du chat syndrome in the United States each year. It can occur in all races and in both sexes.

Signs and symptoms

An abnormal larynx causes the unusual cat-like cry made by infants that is a hallmark feature of the syndrome. As children with cri du chat get older, the cat-like cry becomes less noticeable. This can make the diagnosis more difficult in older patients. In addition to the cat-like cry, individuals with cri du chat also have unusual facial features. These facial differences can be very subtle or more obvious. Microcephaly (small head size) is common. During infancy, many patients with cri du chat do not gain weight or grow normally. Approximately 30% of infants with cri du chat have a congenital heart defect. Hypotonia (poor muscle tone) is also common, leading to problems with eating, and slow normal development. Mental retardation is present in all patients with cri du chat but the degree of mental retardation varies between patients.

Diagnosis

During infancy the diagnosis of cri du chat syndrome is strongly suspected if the characteristic cat-like cry is heard. If a child has this unusual cry or other features seen in cri du chat syndrome, chromosome testing should be performed. Chromosome analysis provides the definitive diagnosis of cri du chat syndrome and can be performed from a blood test. Chromosome analysis, also called "karyotyping", involves staining the chromosomes and examining them under a microscope. In some cases the deletion of material from chromosome 5 can be easily seen. In other cases, further testing must be performed. FISH (fluorescence in-situ hybridization) is a special technique that detects very small deletions. The majority of the deletions that cause cri du chat syndrome can be identified using the FISH technique.

Cri du chat syndrome can be detected before birth if the mother undergoes **amniocentesis** testing or chorionic villus sampling (CVS). This testing would only be recommended if the mother or father is known to have a chromosome rearrangement, or if they already have a child with cri du chat syndrome.

Treatment and management

Currently, there is no cure for cri du chat syndrome. Treatment consists of supportive care and developmental therapy.

Prognosis

Individuals with cri du chat have a 10% mortality during infancy due to complications associated with congenital heart defects, hypotonia, and feeding difficulties. Once these problems are controlled, most individuals with cri du chat syndrome have a normal lifespan. The degree of mental retardation can be severe. However, a recent study suggested that the severity is somewhat affected by the amount of therapy received.

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ORGANIZATIONS

5p- Society. 7108 Katella Ave. #502, Stanton, CA 90680. (888) 970-0777. <http://www.fivepminus.org>.

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

Cri du Chat Society. Dept. of Human Genetics, Box 33, MCV Station, Richmond VA 23298. (804) 786-9632.

Cri du Chat Syndrome Support Group. <http://www.criduchat.u-net.com>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

OMIM—Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov/Omim/>.

Holly Ann Ishmael, MS, CGC

Crouzon craniofacial dysostosis *see* **Crouzon syndrome**

Crouzon syndrome

Definition

Crouzon syndrome is a genetic condition that causes early closure of the bones in the skull. This event is called **craniosynostosis** and causes the skull to be formed differently in affected individuals. Because of the craniosynostosis, individuals affected with Crouzon syndrome will have the characteristic facial features described below.

Description

Other features of Crouzon syndrome include wide-set and prominent eyes. Individuals with this syndrome may also have a condition called strabismus, which means the eyes have difficulty focusing on objects. Other facial features may include an underdeveloped upper jaw, which causes tooth abnormalities. Individuals with Crouzon syndrome often have a beak-shaped nose and hearing loss. A skin condition, called acanthosis nigricans, occurs in approximately 5% of individuals with Crouzon syndrome. It is important to note that there is a wide range of severity in Crouzon syndrome. No two individuals with the condition will necessarily have all the listed features.

It is rare for individuals with Crouzon syndrome to have learning delays or mental impairments. Affected individuals often undergo several corrective surgeries, increasing the need for continual medical care throughout their lives. This can be very stressful and difficult for individuals and their families. Additionally, since people with Crouzon syndrome have significant facial differences, it may be difficult for them (and their parents) to feel accepted by society. There may be psychological implications, ranging from the affected person feeling bad for "looking different" to the parents having trouble bonding to their child for similar reasons. The psychological impact may be less if there are others in the family with Crouzon syndrome. Having more than one family member with this syndrome may help those affected feel less isolated and give them a stronger support system.

Genetic profile

Crouzon syndrome is caused by mutations in the FGFR2 (location 10q25.3-q26) and FGFR3 (location 4p16.3) genes. Crouzon syndrome is inherited in an autosomal dominant manner. An affected individual has one copy of the FGFR mutation and has a 50% chance to pass it on to each of his or her children, regardless of that child's gender. As of 1997, about 75% of affected people have a family history of Crouzon syndrome, which is typically a parent with the condition. In the remaining 25%, the genetic mutation occurs as a new event in the affected individual, and there is no one in their family with the disease. These new mutations are thought to occur because of advancing paternal age, i.e. the age of the patient's father is a factor. Additionally, there is no increased recurrence risk for Crouzon syndrome above the general population risk when there is no family history of the condition.

FGFR2 and FGFR3 are responsible for the proper growth, movement, and creation of specific cells in the body, known as fibroblasts. Fibroblasts are often part of the bony structures in the body (such as the skull), so problems in fibroblast growth and movement would naturally lead to skull/bone problems. As of 1998, about 95% of patients have an FGFR2 mutation, and 5% have an FGFR3 mutation. However, nearly all of the affected individuals that also have acanthosis nigricans have one common FGFR3 mutation.

Demographics

As of 2000, Crouzon syndrome occurs in about one per 25,000 live births. It affects all ethnic groups equally.

Signs and symptoms

There commonly is bilateral (two-sided) coronal craniosynostosis in Crouzon syndrome. A cloverleaf skull may be present if the sagittal (long suture going from front to back of the head) and/or lambdoidal (short suture at very back of the head) sutures are involved. This causes the skull shape to be taller than usual, often described as "tower-shaped." The pattern looks like a cloverleaf because the skull is taller, and the sides of the skull and face bulge slightly from right to left. Additionally, the eye orbits are very shallow, causing the eyes to protrude significantly. This eye finding is always present in the condition. Strabismus may be present and eyes may be wide-set, making vision poor. Some individuals may have unexplained difficulties with their vision. The nose can be narrow and beak-shaped, forcing the individual to breathe through their mouth as a result.

The upper jaw may not be formed properly and can cause dentition problems, most commonly a missing tooth. The palate (upper ridge of the mouth) may be high and narrow, causing crowding of the existing teeth. Occasionally, clefting (improper closure) of the lip and palate may occur. Mild to moderate conductive hearing loss (due to abnormal ear structure formation) may occur in a proportion of cases.

Intellectual development is typically within normal limits. Only rare cases have been reported with signifi-

cant mental deficiency. In about 30% of patients, **hydrocephalus** can occur. Hydrocephalus is an accumulation of fluid in the brain and skull, and this may progress or worsen with time. This typically shows up as a general enlarging of the skull. Sometimes the fluid can put increased pressure on various structures of the brain, limiting their growth and development. Hydrocephalus may be an explanation for the few reported cases of Crouzon syndrome with learning problems. Occasionally, seizures may occur in the condition.

Individuals with Crouzon syndrome may be shorter than the normal expected height. This seems to affect females with the condition more than males.

Diagnosis

Historically, Crouzon syndrome has been diagnosed after careful physical examination and further studies. A diagnosis of Crouzon syndrome can be made through observing several of the following features. The abnormally shaped head is typically seen right away, in the newborn period. It may sometimes be seen in the prenatal period with an ultrasound examination. X-ray or physical examination of the skull can diagnose craniosynostosis. Once craniosynostosis is seen, it is important to determine whether it occurred because of abnormal biology of the cranial suture, possibly caused by an FGFR mutation. This is known as primary craniosynostosis and would make Crouzon syndrome a possibility. Craniosynostosis may also be caused by abnormal outside forces (known as secondary craniosynostosis) such as decreased brain growth or abnormal fetal head positioning. This may have occurred in the prenatal period, and in these cases the abnormal head shape may correct itself with time. The next step is to determine the type of craniosynostosis. A cloverleaf skull makes Crouzon syndrome a possibility, but it is also seen more commonly in other genetic craniosynostosis syndromes.

Some babies with Crouzon syndrome have breathing problems in the newborn period, due to narrowed nasal passages. Protruding eyes are a hallmark feature for the condition, and can be seen almost immediately after birth. The lack of abnormalities in the extremities (hands and feet) are also considered part of the diagnosis of Crouzon syndrome versus another type of craniosynostosis.

As of 2001, molecular (DNA-based) **genetic testing** to diagnose Crouzon syndrome is available at a few laboratories. This testing is specific for the condition, separating it from other craniosynostosis syndrome possibilities. A blood or other type of sample (such as fetal cells from amniotic fluid) from the affected individual is provided, and the FGFR2 **gene** is analyzed.

Abnormal results occur when a mutation in the sequence of the FGFR2 **DNA** is identified from genetic analysis. This means that the mutation caused the symptoms in the individual, confirming the diagnosis of Crouzon syndrome. As mentioned earlier, not every person with Crouzon syndrome will have an FGFR2 mutation. Therefore, one could conceivably go through genetic testing and have no mutation found. This could mean that the person's symptoms are not caused by Crouzon syndrome.

As of 2001, only a little more than 50% of the mutations that cause Crouzon syndrome are known. Therefore, a negative result could also mean that the patient has a genetic mutation that is unable to be found by current technology. Once a mutation is found in a family, it is much easier (and less time-consuming) to test others in the same family. For people with the features of Crouzon syndrome and acanthosis nigricans, there is DNA-based testing to determine if they have the common FGFR3 mutation.

Prenatal testing is available for both FGFR2 and FGFR3 mutations, done via **amniocentesis** or chorionic villus sampling (CVS). This is only offered when there is a parent with a *known* mutation. However, knowing prenatally that an individual has a mutation tells nothing about the extent of the disease. The only way to determine the severity of Crouzon syndrome is by seeing the individual after birth, not by molecular testing. A prenatal ultrasound can sometimes make a possible diagnosis of a syndrome involving craniosynostosis, but it is not as accurate as direct DNA testing. Additionally, a cloverleaf skull seen on a prenatal ultrasound usually implies a more severe outcome for the baby than other types of craniosynostosis.

Treatment and management

Treatment of individuals with Crouzon syndrome often involves the coordinated efforts of several medical specialists in a team setting. The specialists may include a pediatrician, plastic surgeon, neurosurgeon, geneticist, genetic counselor, dentist, social worker, audiologist, speech pathologist, psychologist, and otolaryngologist.

Craniosynostosis is typically repaired through a series of operations. There is a major surgery performed as early as the first three months of life, followed by several others that may extend over the lifespan. Each series of operations is tailored to the individual, but it is rare for the correction to be "perfect" despite the interventions. Because the skull is continually growing in the early part of life, timing of these surgeries is critical for proper brain formation and better results. Surgeries after the skull has stopped growing rarely yield good results.

KEY TERMS

Acanthosis nigricans—A skin condition characterized by darkly pigmented areas of velvety wart-like growths. Acanthosis nigricans usually affects the skin of the armpits, neck, and groin.

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Coronal suture—Skull suture that lies behind the forehead area, across the head from left side to the right side.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Otolaryngologist—Physician who specializes in the care of the ear, nose, and throat and their associated structures.

Strabismus—An improper muscle balance of the ocular musles resulting in crossed or divergent eyes.

Suture—"Seam" that joins two surfaces together.

Surgeries performed before various portions of the facial region have stopped growing also have a poor prognosis, and will require additional follow-up procedures.

For individuals with hydrocephalus, sometimes a shunt, or tube, needs to be placed in order to allow the fluid to drain from the affected area(s) of the brain.

For babies with respiratory distress, oxygen and ventilation are often provided. Occasionally, a tracheostomy (opening in the windpipe) is created to help the individual breathe.

Because their eyes protrude so significantly, people with Crouzon syndrome sometimes have trouble closing their eyes. Surgical eye closure may be necessary, which allows the eye and its various structures (such as the cornea) to remain protected.

Occasionally, surgeries to correct structural ear abnormalities (resulting in hearing loss) are necessary.

Prognosis

The most problematic complication in Crouzon syndrome is the craniosynostosis. Prognosis primarily depends upon the severity and extent of this skull abnormality. Consequently, the success of corrective surgeries often determines prognosis.

Resources

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ORGANIZATIONS

AboutFace USA. PO Box 458, Crystal Lake, IL 60014. (312) 337-0742 or (888) 486-1209. aboutface2000@aol.com. <http://www.aboutface2000.org>.

American Cleft Palate-Craniofacial Association. 104 South Estes Dr., Suite 204, Chapel Hill, NC 27514. (919) 993-9044. Fax: (919) 933-9604. <http://www.cleftline.org>.

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

Crouzon Support Network. PO Box 1272, Edmonds, WA 98020. penny@crouzon.org. <http://www.crouzon.org>.

Crouzon's/Meniere's Parent Support Network. 3757 North Catherine Dr., Prescott Valley, AZ 86314-8320. (800) 842-4681. katy@northlink.com.

WEBSITES

"Craniofacial Anomalies." *Columbia Presbyterian Medical Center Neurological Institute.* <http://cpmcnet.columbia.edu/dept/nsg/PNS/Craniofacial.html>.

Deepti Babu, MS

Cryptophthalmos syndactyly syndrome *see* **Fraser syndrome**

Cutis-gyrata syndrome of Beare and Stevenson *see* **Beare-Stevenson cutis gyrata syndrome**

Cystathionine beta-synthetase *see* **Homocystinuria**

Cystic fibrosis

Definition

Cystic fibrosis (CF) is an inherited disease that affects the lungs, digestive system, sweat glands, and male fertility. Its name derives from the fibrous scar tissue that develops in the pancreas, one of the principal organs affected by the disease.

Description

Cystic fibrosis affects the body's ability to move salt and water in and out of cells. This defect causes the lungs and pancreas to secrete thick mucus, blocking passageways and preventing proper function.

CF affects approximately 30,000 children and young adults in the United States, and about 3,000 babies are born with CF every year. CF primarily affects people of white northern European descent; rates are much lower in non-white populations.

Many of the symptoms of CF can be treated with drugs or nutritional supplements. Close attention to and prompt treatment of respiratory and digestive complications have dramatically increased the expected life span of a person with CF. Several decades ago most children with CF died by age two years; today, about half of all people with CF live past age 31. That median age is expected to grow as new treatments are developed, and it is estimated that a person born in 1998 with CF has a median expected life span of 40 years.

Genetic profile

Cystic fibrosis is a genetic disease, meaning it is caused by a defect in the person's genes. Genes, found in the nucleus of all the body's cells, control cell function by serving as the blueprint for the production of proteins. Proteins carry out a wide variety of functions within cells. The **gene** that, when defective, causes CF is called the CFTR gene, which stands for cystic fibrosis transmembrane conductance regulator. A simple change in this gene leads to all the consequences of CF. There are over 500 known changes in the CFTR gene that can cause CF. However, 70% of all people with an abnormal CFTR gene have the same defect, known as delta-F508.

Genes can be thought of as long strings of chemical words, each made of chemical letters, called nucleotides. Just as a sentence can be changed by rearranging its letters, genes can be mutated, or changed, by changes in the sequence of their nucleotide letters. The gene changes in CF are called point mutations, meaning that the gene is mutated only at one small spot along its length. In other words, the delta-F508 mutation is a loss of one "letter" out of thousands within the CFTR gene. As a result, the CFTR protein made from its blueprint is made incorrectly, and cannot perform its function properly.

The CFTR protein helps to produce mucus. Mucus is a complex mixture of salts, water, sugars, and proteins that cleanses, lubricates, and protects many passageways in the body, including those in the lungs and pancreas. The role of the CFTR protein is to allow chloride ions to exit the mucus-producing cells. When the chloride ions leave these cells, water follows, thinning the mucus. In this way, the CFTR protein helps to keep mucus from becoming thick and sluggish, thus allowing the mucus to be moved steadily along the passageways to aid in cleansing.

In CF, the CFTR protein does not allow chloride ions out of the mucus-producing cells. With less chloride leaving, less water leaves, and the mucus becomes thick and sticky. It can no longer move freely through the passageways, so they become clogged. In the pancreas, clogged passageways prevent secretion of digestive enzymes into the intestine, causing serious impairment of digestion—especially of fat—which may lead to malnutrition. Mucus in the lungs may plug the airways, preventing good air exchange and, ultimately, leading to emphysema. The mucus is also a rich source of nutrients for bacteria, leading to frequent infections.

To understand the **inheritance** pattern of CF, it is important to realize that genes actually have two functions. First, as noted above, they serve as the blueprint for the production of proteins. Second, they are the material of inheritance: parents pass on characteristics to their children by combining the genes in egg and sperm to make a new individual.

Each person actually has two copies of each gene, including the CFTR gene, in each of his or her body cells. During sperm and egg production, however, these two copies separate, so that each sperm or egg contains only one copy of each gene. When sperm and egg unite, the newly created cell once again has two copies of each gene.

The two gene copies may be the same or they may be slightly different. For the CFTR gene, for instance, a person may have two normal copies, or one normal and one mutated copy, or two mutated copies. A person with two mutated copies will develop cystic fibrosis. A person with one mutated copy is said to be a carrier. A carrier will not have symptoms of CF, but can pass on the mutated CFTR gene to his or her children.

When two carriers have children, they have a one in four chance of having a child with CF each time they conceive. They have a two in four chance of having a

KEY TERMS

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

CFTR—Cystic fibrosis transmembrane conductance regulator. The protein responsible for regulating chloride movement across cells in some tissues. When a person has two defective copies of the CFTR gene, cystic fibrosis is the result.

Emphysema—A chronic lung disease that begins with breathlessness during exertion and progresses to shortness of breath at all times, caused by destructive changes in the lungs.

Mucociliary escalator—The coordinated action of tiny projections on the surfaces of cells lining the respiratory tract, which moves mucus up and out of the lungs.

Mucolytic—An agent that dissolves or destroys mucin, the chief component of mucus.

Pancreatic insufficiency—Reduction or absence of pancreatic secretions into the digestive system due to scarring and blockage of the pancreatic duct.

child who is a carrier, and a one in four chance of having a child with two normal CFTR genes.

Approximately one in every 25 Americans of northern European descent is a carrier of the mutated CF gene, while only one in 17,000 African-Americans and one in 30,000 Asian-Americans are carriers. Since carriers are symptom-free, very few people will know whether or not they are carriers, unless there is a family history of the disease. Two white Americans with no family history of CF have a one in 2,500 chance of having a child with CF.

It may seem puzzling that a mutated gene with such harmful consequences would remain so common; one might guess that the high mortality of CF would quickly lead to loss of the mutated gene from the population. Some researchers now believe the reason for the persistence of the CF gene is that carriers, those with only one copy of the gene, are protected from the full effects of cholera, a microorganism that infects the intestine, causing intense diarrhea and eventual death by dehydration. It is believed that having one copy of the CF gene is enough to prevent the full effects of cholera infection, while not enough to cause the symptoms of CF. This so-called "heterozygote advantage" is seen in some other **genetic disorders**, including sickle-cell anemia.

Signs and symptoms

The most severe effects of cystic fibrosis are seen in two body systems: the gastrointestinal (digestive) system and the respiratory tract, from the nose to the lungs. CF also affects the sweat glands and male fertility. Symptoms develop gradually, with gastrointestinal symptoms often the first to appear.

Gastrointestinal system

Ten to fifteen percent of babies who inherit CF have meconium ileus at birth. Meconium is the first dark stool that a baby passes after birth; ileus is an obstruction of the digestive tract. The meconium of a newborn with meconium ileus is thickened and sticky, due to the presence of thickened mucus from the intestinal glands. Meconium ileus causes abdominal swelling and vomiting, and often requires surgery immediately after birth. Presence of meconium ileus is considered highly indicative of CF. Borderline cases may be misdiagnosed, however, and attributed instead to a "milk allergy."

Other abdominal symptoms are caused by the inability of the pancreas to supply digestive enzymes to the intestine. During normal digestion, as food passes from the stomach into the small intestine, it is mixed with pancreatic secretions, which help to break down the nutrients for absorption. While the intestines themselves also provide some digestive enzymes, the pancreas is the major source of enzymes for the digestion of all types of foods, especially fats and proteins.

In CF, thick mucus blocks the pancreatic duct, which is eventually closed off completely by scar tissue formation, leading to a condition known as pancreatic insufficiency. Without pancreatic enzymes, large amounts of undigested food pass into the large intestine. Bacterial action on this rich food source can cause gas and abdominal swelling. The large amount of fat remaining in the feces makes it bulky, oily, and foul-smelling.

Because nutrients are only poorly digested and absorbed, the person with CF is often ravenously hungry, underweight, and shorter than expected for his age. When CF is not treated for a longer period, a child may develop symptoms of malnutrition, including anemia, bloating, and, paradoxically, appetite loss.

Diabetes becomes increasingly likely as a person with CF ages. Scarring of the pancreas slowly destroys those pancreatic cells which produce insulin, producing type I, or insulin-dependent, diabetes.

Gallstones affect approximately 10% of adults with CF. Liver problems are less common, but can be caused by the build-up of fat within the liver. Complications of liver enlargement may include internal hemorrhaging,

abdominal fluid (ascites), spleen enlargement, and liver failure.

Other gastrointestinal symptoms can include a prolapsed rectum, in which part of the rectal lining protrudes through the anus; intestinal obstruction; and rarely, intussusception, in which part of the intestinal tube slips over an adjoining part, cutting off blood supply.

Somewhat fewer than 10% of people with CF do not have gastrointestinal symptoms. Most of these people do not have the delta-F508 mutation, but rather a different one, which presumably allows at least some of their CFTR proteins to function normally in the pancreas.

Respiratory tract

The respiratory tract includes the nose, the throat, the trachea (or windpipe), the bronchi (which branch off from the trachea within each lung), the smaller bronchioles, and the blind sacs called alveoli, in which gas exchange takes place between air and blood.

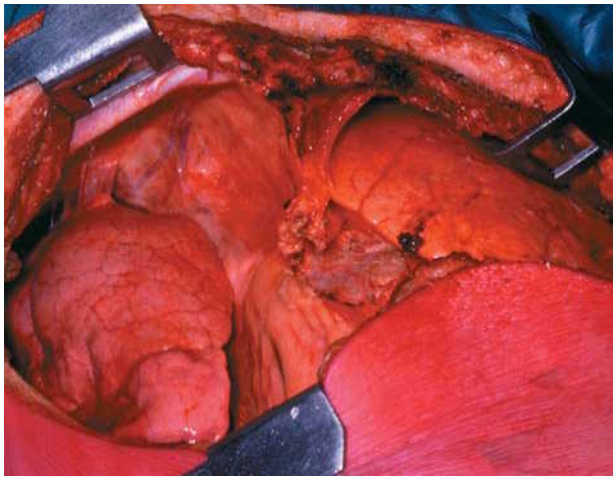
Swelling of the sinuses within the nose is common in people with CF. This usually shows up on x ray, and may aid the diagnosis of CF. However, this swelling, called pansinusitis, rarely causes problems, and does not usually require treatment.

Nasal polyps, or growths, affect about one in five people with CF. These growths are not cancerous, and do not require removal unless they become annoying. While nasal polyps appear in older people without CF, especially those with allergies, they are rare in children without CF.

The lungs are the site of the most life-threatening effects of CF. The production of a thick, sticky mucus increases the likelihood of infection, decreases the ability to protect against infection, causes inflammation and swelling, decreases the functional capacity of the lungs, and may lead to emphysema. People with CF will live with chronic populations of bacteria in their lungs, and lung infection is the major cause of death for those with CF.

The bronchioles and bronchi normally produce a thin, clear mucus, which traps foreign particles including bacteria and viruses. Tiny hair-like projections called cilia on the surface of these passageways slowly sweep the mucus along, out of the lungs and up the trachea to the back of the throat, where it may be swallowed or coughed up. This “mucociliary escalator” is one of the principal defenses against lung infection.

The thickened mucus of CF prevents easy movement out of the lungs, and increases the irritation and inflammation of lung tissue. This inflammation swells the passageways, partially closing them down, further hampering the movement of mucus. A person with CF is likely to cough more frequently and more vigorously as the lungs attempt to clean themselves out.

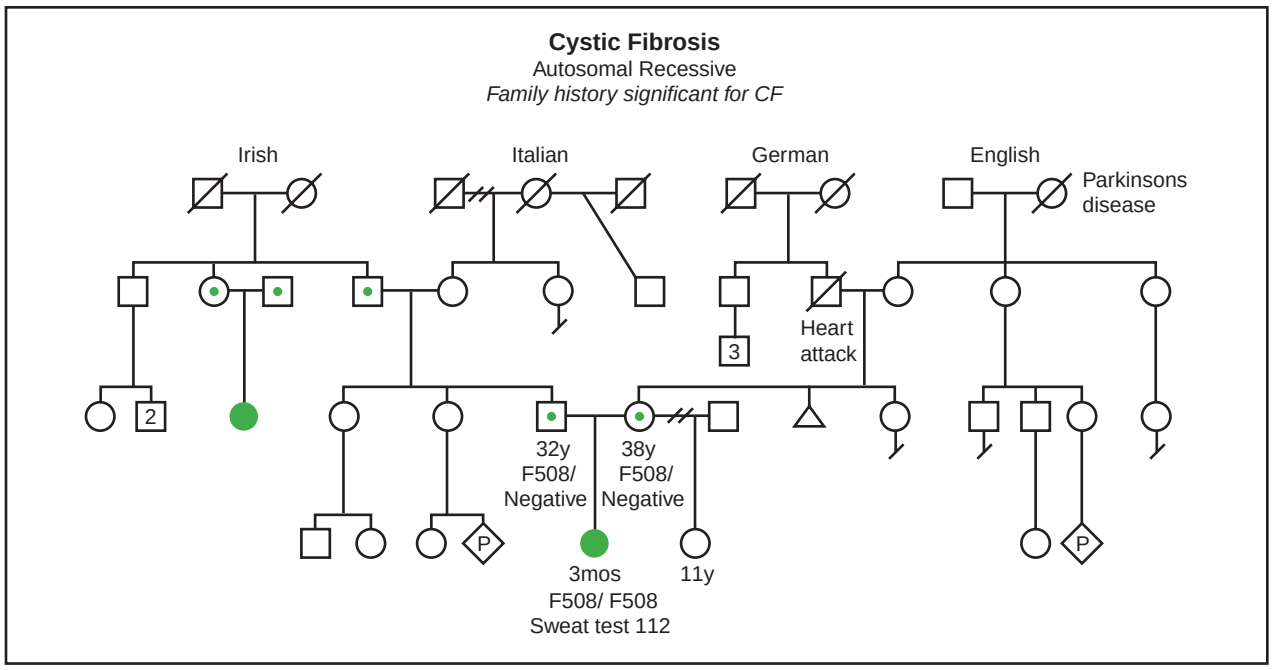


Accumulation of mucus in the smaller passageways of the lungs can plug them up, decreasing functional lung volume. As the air is exhaled, much of it becomes trapped in the small pores of the lungs. This leads to expansion of the lung and swollen appearance seen in the left lung above. *(Custom Medical Stock Photo, Inc.)*

At the same time, infection becomes more likely since the mucus is a rich source of nutrients. Bronchitis, bronchiolitis, and pneumonia are frequent in CF. The most common infecting organisms are the bacteria *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. A small percentage of people with CF have infections caused by *Burkholderia cepacia*, a bacterium which is resistant to most current antibiotics (*Burkholderia cepacia* was formerly known as *Pseudomonas cepacia*). The fungus *Aspergillus fumigatus* may infect older children and adults.

The body’s response to infection is to increase mucus production; white blood cells fighting the infection thicken the mucus even further as they break down and release their cell contents. These white blood cells also provoke more inflammation, continuing the downward spiral that marks untreated CF.

As mucus accumulates, it can plug up the smaller passageways in the lungs, decreasing functional lung volume. Getting enough air can become difficult; tiredness, shortness of breath, and intolerance of exercise become more common. Because air passes obstructions more easily during inhalation than during exhalation, over time, air becomes trapped in the smallest chambers of the lungs, the alveoli. As millions of alveoli gradually expand, the chest takes on the enlarged, barrel-shaped appearance typical of emphysema.



(Gale Group)

For unknown reasons, recurrent respiratory infections lead to "digital clubbing," in which the last joint of the fingers and toes becomes slightly enlarged.

Sweat glands

The CFTR protein helps to regulate the amount of salt in sweat. People with CF have sweat that is much saltier than normal, and measuring the saltiness of a person's sweat is the most important diagnostic test for CF. Parents may notice that their infants taste salty when they kiss them. Excess salt loss is not usually a problem except during prolonged exercise or heat. While most older children and adults with CF compensate for this extra salt loss by eating more salty foods, infants and young children are in danger of suffering its effects (such as heat prostration), especially during summer. Heat prostration is marked by lethargy, weakness, and loss of appetite, and should be treated as an emergency condition.

Fertility

Ninety-eight percent of men with CF are sterile, due to complete obstruction or absence of the vas deferens, the tube carrying sperm out of the testes. While boys and men with CF form normal sperm and have normal levels of sex hormones, sperm are unable to leave the testes, and fertilization is not possible. Most women with CF are fertile, though they often have more trouble getting pregnant than women without CF. In both boys and girls, puberty is often delayed, most likely due to the effects of poor nutrition or chronic lung infection. Women with good lung health usually have no problems with pregnancy, while those with ongoing lung infection often do poorly.

Diagnosis

The decision to test a child for cystic fibrosis may be triggered by concerns about recurring gastrointestinal or respiratory symptoms, or salty sweat. A child born with meconium ileus will be tested before leaving the hospital. Families with a history of CF may wish to have all children tested, especially if there is a child who already has the disease. Some hospitals now require routine screening of newborns for CF.

Sweat test

The sweat test is both the easiest and most accurate test for CF. In this test, a small amount of the drug pilocarpine is placed on the skin. A very small electrical current is then applied to the area, which drives the pilocarpine into the skin. The drug stimulates sweating in the treated area. The sweat is absorbed onto a piece of filter paper, and is then analyzed for its salt content. A person with CF will have salt concentrations that are one-and-one-half to two times greater than normal. The test can be done on persons of any age, including newborns, and its results can be determined within an hour. Virtually every person who has CF will test positively on it, and virtually everyone who does not will test negatively.

Genetic testing

The discovery of the CFTR gene in 1989 allowed the development of an accurate genetic test for CF. Genes from a small blood or tissue sample are analyzed for specific mutations; presence of two copies of the mutated gene confirms the diagnosis of CF in all but a very few cases. However, since there are so many different possible mutations, and since testing for all of them would be too expensive and time-consuming, a negative gene test cannot rule out the possibility of CF.

Couples planning a family may decide to have themselves tested if one or both have a family history of CF. Prenatal **genetic testing** is possible through **amniocentesis**. Many couples who already have one child with CF decide to undergo prenatal screening in subsequent pregnancies. Siblings in these families are also usually tested, both to determine if they will develop CF, and to determine if they are carriers, to aid in their own family planning. If the sibling has no symptoms, determining his or her carrier status is often delayed until the teen years or later, when he or she is closer to needing the information to make decisions.

Newborn screening

Some states now require screening of newborns for CF, using a test known as the IRT test. This is a blood test which measures the level of immunoreactive trypsinogen, which is generally higher in babies with CF than those without it. This test gives many false positive results immediately after birth, and so requires a second test several weeks later. A second positive result is usually followed by a sweat test.

Treatment and management

There is no cure for cystic fibrosis. Treatment has advanced considerably in the past several decades, increasing both the life span and the quality of life for most people affected by CF. Early diagnosis is important to prevent malnutrition and infection from weakening the young child. With proper management, many people with CF engage in the full range of school and sports activities.

Nutrition

People with CF usually require high-calorie diets and vitamin supplements. Height, weight, and growth of a person with CF are monitored regularly. Most people with CF need to take pancreatic enzymes to supplement or replace the inadequate secretions of the pancreas. Tablets containing pancreatic enzymes are taken with every meal; depending on the size of the tablet and the meal, as many as 20 tablets may be needed. Because of incomplete absorption even with pancreatic enzymes, a person with CF needs to take in about 30% more food than a person without CF. Low-fat diets are *not* recommended except in special circumstances, since fat is a source of both essential fatty acids and abundant calories.

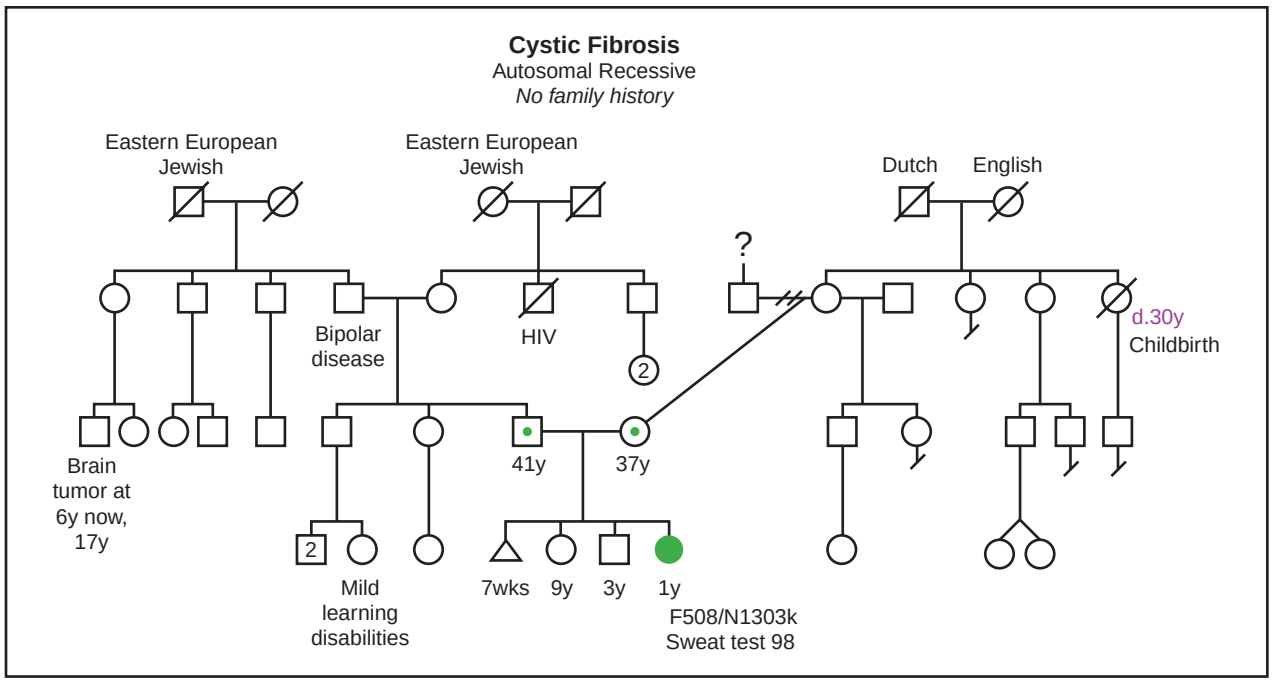
Some people with CF cannot absorb enough nutrients from the foods they eat, even with specialized diets and enzymes. For these people, tube feeding is an option. Nutrients can be introduced directly into the stomach through a tube inserted either through the nose (a nasogastric tube) or through the abdominal wall (a gastrostomy tube). A jejunostomy tube, inserted into the small intestine, is also an option. Tube feeding can provide nutrition at any time, including at night while the person is sleeping, allowing constant intake of high-quality nutrients. The feeding tube may be removed during the day, allowing normal meals to be taken.

Respiratory health

The key to maintaining respiratory health in a person with CF is regular monitoring and early treatment. Lung function tests are done frequently to track changes in functional lung volume and respiratory effort. Sputum samples are analyzed to determine the types of bacteria present in the lungs. Chest x rays are usually taken at least once a year. Lung scans, using a radioactive gas, can show closed off areas not seen on the x ray. Circulation in the lungs may be monitored by injection of a radioactive substance into the bloodstream.

People with CF live with chronic bacterial colonization; that is, their lungs are constantly host to several species of bacteria. Good general health, especially good nutrition, can keep the immune system healthy, which decreases the frequency with which these colonies begin an infection, or attack on the lung tissue. Exercise is another important way to maintain health, and people with CF are encouraged to maintain a program of regular exercise.

In addition, clearing mucus from the lungs helps to prevent infection, and mucus control is an important aspect of CF management. Bronchial drainage is used to allow gravity to aid the mucociliary escalator. For this technique, the person with CF lies on a tilted surface with head downward, alternately on the stomach, back, or side, depending on the section of lung to be drained. An assistant thumps the rib cage to help loosen the secretions. A device called a “flutter” offers another way to loosen secretions: it consists of a stainless steel ball in a tube. When a person exhales through it, the ball vibrates, sending vibrations back through the air in the lungs. Some special breathing techniques may also help clear the lungs.



(Gale Group)

Several drugs are available to prevent the airways from becoming clogged with mucus. Bronchodilators can help open up the airways; steroids reduce inflammation; and mucolytics loosen secretions. Acetylcysteine (Mucomyst) has been used as a mucolytic for many years but is not prescribed frequently now, while DNase (Pulmozyme) is a newer product gaining in popularity. DNase breaks down the **DNA** from dead white blood cells and bacteria found in thick mucus.

People with CF may pick up bacteria from other CF patients. This is especially true of *Burkholderia cepacia*, which is not usually found in people without CF. While the ideal recommendation from a health standpoint might be to avoid contact with others who have CF, this is not usually practical (since CF clinics are a major site of care), nor does it meet the psychological and social needs of many people with CF. At a minimum, CF centers recommend avoiding prolonged close contact between people with CF, and scrupulous hygiene, including frequent hand washing. Some CF clinics schedule appointments on different days for those with and without *B. cepacia* colonies.

Some doctors choose to prescribe antibiotics only during infection, while others prefer long-term antibiotic treatment against *S. aureus*. The choice of antibiotic depends on the particular organism or organisms found. Some antibiotics are given as aerosols directly into the lungs. Antibiotic treatment may be prolonged and aggressive.

Supplemental oxygen may be needed as lung disease progresses. Respiratory failure may develop, requiring temporary use of a ventilator to perform the work of breathing.

Lung transplantation is another option for people with CF, although the number of people who receive them is still much lower than those who want them. Transplantation is not a cure, however, and has been likened to trading one disease for another. Long-term immunosuppression is required, increasing the likelihood of other types of infection. About 50% of adults and more than 80% of children who receive lung transplants live longer than two years. Some CF patients whose livers have been damaged by fibrosis also undergo liver transplants.

Long-term use of ibuprofen has been shown to help some people with CF; presumably by reducing inflammation in the lungs. Close medical supervision is necessary, however, since the effective dose is high and not everyone benefits. Ibuprofen at the required doses interferes with kidney function, and together with aminoglycoside antibiotics, may cause kidney failure.

A number of experimental treatments are currently the subject of much research. Some evidence indicates that aminoglycoside antibiotics may help overcome the genetic defect in some CF mutations, allowing the protein to be made normally. While promising, these results would apply to only about 5% of those with CF.

Gene therapy is currently the most ambitious approach to curing CF. In this set of techniques, non-defective copies of the CFTR gene are delivered to affected cells, where they are taken up and used to create the CFTR protein. While elegant and simple in theory, gene therapy has met with a large number of difficulties in trials so far, including immune resistance, very short duration of the introduced gene, and inadequately widespread delivery.

Alternative treatment

In homeopathic medicine, the symptoms of the disease would be addressed to enhance the quality of life for the person with cystic fibrosis. Treating the cause of CF, because of the genetic basis for the disease, is not possible. Homeopathic medicine seeks to treat the whole person, however, and in cystic fibrosis, this approach might include:

- Mucolytics to help thin mucous.
- Supplementation of pancreatic enzymes to assist in digestion.
- Respiratory symptoms can be addressed to open lung passages.
- Hydrotherapy techniques to help ease the respiratory symptoms and help the body eliminate mucus.
- Immune enhancements can help prevent the development of secondary infections.
- Dietary enhancements and adjustments are used to treat digestive and nutritional problems.

Prognosis

People with CF may lead relatively normal lives. The possible effect of pregnancy on the health of a woman with CF requires careful consideration before beginning a family, as do issues of longevity, and their children's status as carriers. Although most men with CF are functionally sterile, new procedures for removing sperm from the testes are being tried, and may offer more men the chance to become fathers.

Approximately half of people with CF live past the age of 30. Because of better and earlier treatment, a person born today with CF is expected, on average, to live to age 40.

Resources

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Cystic Fibrosis Foundation. 6931 Arlington Rd., Bethesda, MD 20814. (301) 951-4422. <http://www.cff.org>.

WEBSITES

Cystic Fibrosis Information. <http://cf-web.mit.edu/index.html>.

Edward Rosick, DO, MPH, MS

Cystinosis

Definition

Cystinosis is a rare genetic metabolic disease that causes cystine, an amino acid, to accumulate in lysosomes of various organs of the body such as the kidneys, liver, eyes, muscles, pancreas, brain, and white blood cells. Although cystinosis primarily affects children, a form of the disease also occurs in adults.

Description

In cystinosis, the cystine content of cells increases to an average of 50 to 100 times its normal value. This increase is caused by an abnormality in the transport of cystine out of a sac-like compartment of the cell called the lysosome. Because of cystine's low solubility in water, this amino acid forms crystals that accumulate within the lysosomes of cells. The accumulation of cystine is believed to destroy the cells.

There are three basic forms of cystinosis: infantile nephropathic cystinosis; late-onset nephropathic cystinosis; and benign non-nephropathic cystinosis.

Infantile nephropathic cystinosis

Children with infantile cystinosis usually appear normal at birth and during the first six to eight months of life. As Fanconi's syndrome (a tubular dysfunction of the kidneys causing an impairment in the kidneys' ability to reabsorb minerals and nutrients back into the bloodstream) develops, sodium and water depletion occurs, leading to polyuria (excessive urination) and polydipsia (excessive thirst). Affected children become especially vulnerable to dehydration. This tubular abnormality, in addition to an abnormality in sweat production, often leads to recurrent fevers as a presenting symptom.

By one year of age, children generally exhibit growth retardation, rickets (inadequate deposition of minerals in developing cartilage and newly formed bone,

causing abnormalities in shape and structure of bones), metabolic acidosis (excessive acid in the blood), and other chemical evidence or renal tubular abnormalities of the kidney, such as increased renal (kidney) excretion of glucose, amino acids, phosphate, and potassium. However, more subtle clinical and biochemical evidence of the disease can be detected at a much earlier age by careful examination of at-risk children (those with a sibling or other relative with the disease). As a child with infantile nephropathic cystinosis ages, failure to thrive is apparent.

Without therapeutic intervention, children remain below the norm in both height and weight throughout life. The typical patient with infantile nephropathic cystinosis has short stature, retinopathy (retinal disorder), photophobia (light sensitivity), and onset of Fanconi's syndrome in the first year of life. By one to two years of age, corneal cystine crystals and rickets are evident. Glomerular failure (the glomerulus is a small structure in the kidney made up of a cluster of capillaries) progresses, and end-stage renal disease occurs by about nine to ten years of age.

Late-onset cystinosis

In late-onset nephropathic cystinosis, the age of onset ranges from 2–26 years; however, the typical age at which this condition presents is 12–13 years. If more than one sibling develops late-onset cystinosis, their age of onset and symptoms are generally similar. Patients with this condition develop crystalline deposits in the cornea and conjunctiva (mucous membrane lining the eyelids) as well as in the bone marrow. Although patients with late-onset cystinosis often do not develop full-blown Fanconi's syndrome, **renal failure** progresses to such a degree that kidney transplantation is necessary, as in the case of infantile nephropathic cystinosis. These individuals are usually in end-stage renal failure within a few years of diagnosis.

Benign non-nephropathic cystinosis

Formerly known as adult cystinosis, benign non-nephropathic cystinosis is usually discovered by chance when an ophthalmologic (eye) examination reveals crystalline opacities within the cornea and conjunctiva. As in patients with infantile nephropathic cystinosis, those with benign cystinosis may also have photophobia; however, light sensitivity may not develop until middle age and is usually not as debilitating. Because the only patients diagnosed with benign cystinosis are those who undergo slit-lamp (a lamp constructed such that intense light is emitted through a slit) eye examination, it is possible that many individuals with this form of the disease never experience eye symptoms and are never diagnosed. Patients with benign cystinosis develop crystalline deposits in their bone marrow and white blood cells but do not develop renal dysfunction or retinopathy.

Genetic profile

Cystinosis is an autosomal recessive genetic disease. The term "autosomal" refers to a **gene** situated on one of the 22 of the 23 pairs of **chromosomes** other than a sex chromosome (or the X or Y chromosome). The term "recessive" refers to an allele, or a form of a gene that may be expressed and/or active; however, the "dominant" form of the gene on the other chromosome usually takes over enough of the gene's normal function to prevent symptoms of a disorder. Each parent of a child with cystinosis carries one abnormal (recessive) gene and one normal gene. Thus, the child must inherit an abnormal (or altered) gene from each parent to develop the disease. In addition, when a child develops cystinosis, the parents are almost always surprised because they never exhibited any symptoms of the disease. The recessive gene may lie dormant for generations until two people with the abnormal gene come together and have children.

Each time two such cystinosis carriers—persons with one copy of the altered gene and one copy of a normal or functioning gene—have a child together, there is a one-in-four chance (25% risk) of having a child with cystinosis; two-in-four (50% risk) the child will not have cystinosis but will be a carrier; and a one-in-four chance the child will not have cystinosis or be a carrier. Also, every unaffected sibling of a child with cystinosis has a two-in-three (67%) chance of being a carrier (having one copy of the abnormal gene and one copy of a normal gene), like his or her parents.

Scientists have mapped the cystinosis gene, CTNS, to the short arm of chromosome 17 (at location 17p13). Mutations (changes) in the cystinosis gene (specifically, a deletion of a particular part of the gene) have been found to cause all three types of cystinosis. However, this deletion is difficult to identify in some individuals for reasons that are uncertain. In these individuals, extensive and very sophisticated laboratory work (molecular **genetic testing**) to identify and prove the existence of the deletion would be necessary.

In patients of Northern European descent, for example, there is about a 50/50 probability that an individual with cystinosis has the deletion. Genetic testing is under investigation for populations of these regions, but until details of the methodology are refined, measurement of lysosomal cystine in white cells and fibroblasts (any cell or corpuscle from which connective tissue is developed) will remain the state-of-the art and the most broadly based general method for diagnosing cystinosis.

Demographics

It is estimated that 2,000 individuals worldwide have cystinosis, although exact figures are difficult to obtain because the disease often remains undiagnosed. In the United States, the disease is believed to affect approximately 400 individuals.

Signs and symptoms

Although the symptoms of cystinosis vary, depending on the type of disease present, general symptoms include:

- acidosis
- dehydration
- rickets
- growth retardation
- renal glomerular failure
- corneal ulcerations and retinal blindness
- delayed puberty
- swallowing difficulties

Diagnosis

Cystinosis may be diagnosed prenatally by examining cystine levels in chorionic villi (obtained by chorionic villus sampling, usually done at 10–12 weeks gestation) or in cells contained in amniotic fluid (obtained by **amniocentesis**, usually done at 16–18 weeks gestation). In early infancy, cystinosis is usually diagnosed by measuring free cystine in white blood cells and skin fibroblasts.

Chorionic villus sampling

Chorionic villus sampling (tissue sample of tiny pieces of placental tissue obtained by inserting a thin needle or narrow tube into the uterus) is performed at 10–12 weeks of gestation. Intracellular cystine levels are measured. The values in a fetus with cystinosis are more than 10 times greater than normal.

Amniocentesis

Amniocentesis (sample of amniotic fluid obtained by inserting a thin needle into the uterus) can be performed at 16–18 weeks of gestation.

White blood cell testing

When diagnosed early, the progressive kidney failure, retarded growth, and vision problems can be prevented or delayed by proper management and medication. The metabolic abnormality in cystinosis is the failure of the cellular lysosomes to release cystine. As a result, the free cystine in the lysosomes accumulates to many times the normal value. The diagnosis of cystinosis is therefore based in part on the measurement of free cystine in the tissues that accumulate this amino acid. This measurement is most easily accomplished in white blood cells. Whole blood contains red cells, which are rich in glutathione, a compound that can react with cystine. To prevent this reaction, white cells are separated from red cells. The white cells are kept cold to slow down reactions, then broken open, and frozen. Freezing prevents the reaction of cystine with compounds such as glutathione and precipitates the cell protein. These steps stabilize the cystine content of the preparation.

Skin fibroblast testing

Cultured skin fibroblasts may also be used to diagnose cystinosis. Because of the increased time and costs, white blood cells are usually sent for testing first. Skin fibroblast testing (biopsy) is also more invasive than a blood sample. On rare occasions the expression of the abnormality in white cells is borderline for diagnosis. Thus, confirmation using fibroblasts is definitive.

Treatment and management

Cystinosis is treated by a variety of pharmacologic and nonpharmacologic therapies as well as by surgical transplantation.

Pharmacologic therapy

The aim of specific treatment for cystinosis is to reduce cystine accumulation within the cells. This goal is achieved by cysteamine treatment, which has proven effective in delaying or preventing renal failure. Cysteamine treatment also improves growth in children with cystinosis. The growth improvement with cysteamine bitartrate usually allows the patient to maintain growth along a percentile but does not usually aid in achieving “catch-up” growth.

The Food and Drug Administration (FDA) approved a capsule form of cysteamine bitartrate called Cystagon in August 1994. However, oral cysteamine does not prevent the progression of ocular lesions and has many potential side effects. Little is known about the drug’s long-term effects. The main disadvantage of cysteamine treatment is the need for four daily capsules (every six hours) and the sulfurous breath it causes. Cysteamine treatment is also expensive.

Many children with cystinosis receive growth hormone, and some have had improvements in height. There is also evidence that indomethacin (Indocin) increases

KEY TERMS

Cystine—A sulfur-containing amino acid, sometimes found as crystals in the kidneys or urine, that forms when proteins are broken down by digestion.

Fanconi syndrome—A reabsorbtion disorder in the kidney tubules.

Glomerulus—A structure in the kidney composed of blood vessels that are actively involved in the filtration of the blood.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Nephropathy—Kidney disease.

Photophobia—An extreme sensitivity to light.

Retinopathy—Any disorder of the retina.

appetite, decreases urine volume, decreases water consumption, and improves growth in pretransplanted patients with cystinosis.

Vitamin/mineral supplementation

The symptomatic treatment of the Fanconi's syndrome is essential in patients with cystinosis. The urinary losses of water, salts, bicarbonate, and minerals must be replaced. Most children receive a solution of sodium and potassium citrate, as well as phosphate. Some also receive extra vitamin D.

Organ transplantation

Kidney transplantation has proven useful in patients with cystinosis. If a patient with cystinosis receives a kidney transplant and reaches adulthood, the new kidney will not be affected by the disease. However, without cysteamine treatment, kidney transplant recipients can develop complications in other organs due to the continued cystine accumulation in the body. These complications can include muscle wasting, difficulty swallowing, diabetes, hypothyroidism, and blindness. Not all older patients, however, develop these symptoms.

In both young children with cystinosis and older patients with a kidney transplant, cysteamine eye drops may be useful in removing the corneal cystine crystals and reduce photophobia. However, as of early 2001, the drops have not yet received FDA approval.

Prognosis

Since 1980, the prognosis of a child with cystinosis has greatly improved. However, if children with the disease receive no treatment, they rarely survive past the age of nine or ten.

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Cystinosis Research Network. 8 Sylvester Rd., Burlington, MA 01803. (866) CURE NOW. Fax: (781) 229-6030. <http://www.cystinosis.org>.

National Center for Biotechnology Information. National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894. (301) 496-2475. <http://www3.ncbi.nlm.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Genevieve T. Slomski, PhD

Cystinuria

Definition

Cystinuria is a relatively common inherited disorder characterized by the formation of cystine urinary tract

stones that can lead to obstruction, infection, and eventual loss of renal function.

Description

In cystinuria there is a defect in the movement of cystine and the dibasic amino acids (lysine, arginine, and ornithine) across the epithelial cells of the kidneys and the small intestine. In the kidney, most amino acids are filtered by the glomerulus and reabsorbed by the proximal tubules with little residual amino acid in the urine. In cystinuria, cystine and the dibasic amino acids are not reabsorbed by the tubules of the kidney and eventually build up in the urine. Cystine in high concentrations is insoluble in urine and will form stones (calculi) in the kidneys, bladder, and ureters. The transport defect in the small intestine leads to the accumulation of digestion breakdown products of cystine and the dibasic amino acids in the stool, urine, and plasma. The intestinal defect does not appear to result in any adverse symptoms for the affected individual.

Cystinuria has been classified into three types (I, II, and III) based on the urinary excretion of cystine and the dibasic amino acids among carriers of the disease (heterozygotes) and on the nature of the intestinal transport defect among affected individuals (homozygotes).

The name cystine is derived from the Greek word for bladder, *kystis*. When the disease was first described in the 1800's, it was thought that the origin of the cystine stones was the bladder. Historically, cystinuria is important because it was one of the four inborn errors of metabolism reported by Sir Archibald Garrod in his famous Croonian lectures in 1908. Although alternate names for the disorder include: cistinuria, cystine-lysinuria, cystine-lysine-arginine-ornithinuria and cystinuria dibasic amnioaciduria, the term cystinuria is used most often to describe the disease.

Genetic profile

Cystinuria is a complex autosomal recessive disorder. Type I cystinuria is completely recessive; carriers have no manifestations. Types II and III cystinuria are incompletely recessive; carriers can display symptoms. Two amino acid transporter genes, SLC3A1 (solute carrier family 3, member 1) located on chromosome 2p, and SLC7A9 (solute carrier family 7 member 9) located on chromosome 19q are known to cause cystinuria. The proteins produced by these two genes apparently interact with one another. An individual with two mutations in the SLC3A1 **gene** (homozygote) has type I disease. Mutations in the SLC7A9 gene lead to types II and III cystinuria. Types II and III cystinuria are allelic; different changes (mutations) in the same gene lead to alternative forms of the disease. There are some patients who are genetic compounds, they have a type II mutation on one copy of the gene and a type III mutation on the other copy. There are also individuals who may have mutations in both the SLC3A1 gene and the SLC7A9 gene.

Demographics

Cystinuria is considered one of the more common **genetic disorders** with an estimated prevalence of one in 7,000. Most affected individuals have type I disease. Type II disease is relatively rare. Due to a founder effect, an increased incidence of cystinuria exists among individuals of Libyan Jewish ancestry. Approximately one in 2,500 persons of Libyan Jewish descent has type II disease. The carrier frequency in this population is around one in 25.

Signs and symptoms

Symptoms of cystinuria develop due to the high level of cystine in the urine. Since cystine at high concentrations is insoluble in urine, undissolved cystine accumulates in the urine and affected individuals are prone to recurrent urinary tract stone formation (nephrolithiasis). Also, hexagonal-shaped crystals form in the urine; these crystals signify the presence of cystine in potentially stone-forming concentrations. The onset of cystinuria is variable and symptoms can appear anytime between the first year of life and the ninth decade. Most cystinurics develop symptoms in the second and third decades of life. In many affected individuals the first sign of the disorder is renal colic, a painful condition caused by obstruction of the urinary tract. Obstruction of the urinary tract due to calculi can lead to infection and eventually to renal insufficiency. Less often, complaints such as infection, hypertension, and **renal failure** are the first reasons cystinuric patients seek medical attention.

Unlike most autosomal recessive disorders, carriers for types II and III cystinuria can be symptomatic. Type II carriers have high urinary excretion of cystine and lysine and type II carriers have moderate excretion of cystine, lysine, arginine, and ornithine. Both type II and type III carriers are at-risk to develop stones. Type I carriers have no excess cystine or dibasic amino acids in their urine and are without symptoms of the disorder.

Although there are reports of an association between cystinuria and neurologic abnormalities, little is known about the mechanism responsible for this nor is the prevalence of this complication among affected individuals known.

Diagnosis

The diagnosis of cystinuria is made at the biochemical level. Molecular (genetic) testing is also available but is generally not the first means of making a cystinuria

KEY TERMS

Alkalinization—The process of making a solution more basic, rather than more acidic, by raising the pH.

Allelic—Related to the same gene.

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are "essential amino acids" which the body cannot make and must therefore be obtained from food).

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Catheter—A narrow, flexible tube used to create a pathway for introducing drugs, nutrients, fluids, or blood products into the body and/or for removing fluid or other substances from the body.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cystine—A sulfur-containing amino acid, sometimes found as crystals in the kidneys or urine, that forms when proteins are broken down by digestion.

Epithelial cells—The layer of cells that cover the open surfaces of the body such as the skin and mucous membranes.

Founder effect—Increased frequency of a gene mutation in a population that was founded by a small ancestral group of people, at least one of whom was a carrier of the gene mutation.

Glomerulus—A structure in the kidney composed of blood vessels that are actively involved in the filtration of the blood.

Homozygote—Having two identical copies of a gene or chromosome.

Obligate carrier—An individual who, based on pedigree analysis, must carry a genetic mutation for a particular genetic disease. Parents of a child with an autosomal recessive disorder are obligate carriers.

Oral loading test—A procedure in which cystine is administered orally to a patient and plasma levels of cystine are measured. Under normal circumstances, amino acids are absorbed by the intestine and result in an increase in plasma amino acid levels. However, in cystinuria, there is a problem in the absorption process and blood levels of amino acids do not rise or rise slowly after eating.

Plasma—The liquid part of the blood and lymphatic fluid that contains antibodies and other proteins.

Renal—Related to the kidneys.

Renal colic—A spasmodic pain, moderate to severe in degree, located in the back, side and/or groin area.

Small intestine—The part of the digestive tract in-between the stomach and the large intestine.

Tubule—A small tube lined with glandular epithelium in the kidney.

Ureters—Tubes through which urine is transported from the kidneys to the bladder.

diagnosis. The simplest approach to diagnosis of this condition is microscopic examination of the urine for the characteristic hexagonal-shaped crystals. Urinary microscopic examination was the primary means of cystinuria diagnosis for many years since the discovery of these crystals by Stromeyer in 1824, and it remains a useful aid in the diagnosis of this condition today. Another widely used screening procedure is the cyanide-nitroprusside test, a test that measures the amount of cystine excreted in the urine in comparison to the amount of creatinine (a protein normally found in urine). In those patients who display crystals and have a positive nitroprusside test, further diagnostic tests such as thin-layer chromatography or high-voltage electrophoresis can identify the specific amino acids (cystine, lysine, arginine, ornithine), and other techniques such as ion-exchange chromatography, liquid chromatography-mass spectrophotometer, and high-performance liquid chromatography may be performed to measure the amounts of these amino acids in the urine.

The type (I, II, or II) of cystinuria in an affected patient can be determined by family studies and/or by study of the intestinal transport defect in an affaected individual. Type I obligate carrriers have normal amounts of urinary cystine and dibasic amino acids. Type II carriers have between nine and fifteen times the normal

amount of cystine and lysine in their urine. Type III carriers have up to twice the normal range of cystine and the dibasic amino acids in their urine. The intestinal absorption defect in an affected individual can be demonstrated by oral loading tests and/or by study of the transport of cystine and the dibasic amino acids in an intestinal biopsy specimen from an affected individual.

Testing for mutations in the SLC3A1 gene and the SLC7A9 gene is possible. Over forty mutations in the SLC3A1 gene have been found and almost as many have been detected in the SLC7A9 gene.

Treatment and management

Prevention

The primary goal of treatment of cystinuria is prevention of existing cystine stones through non-invasive means. There are three main categories of treatment: increase cystine solubility, reduce cystine production and excretion, and convert cystine into a more soluble compound. The first step in treatment is to increase cystine solubility via hydration therapy. It is recommended that patients increase their fluid intake such that the concentration of cystine is 200-250 mg/liter of urine. This therapy prevents stone formation approximately two-thirds of the time. Another therapy that increases cystine solubility is known as oral alkalinization. Medications such as sodium citrate, potassium citrate, or sodium bicarbonate increase the pH of urine to levels at which cystine becomes a more soluble compound. To reduce cystine excretion and production, individuals with cystinuria may follow a diet low in sodium and protein.

If the above measures are not successful in preventing stones and/or dissolving existing ones, drug therapy may be necessary. Tiopronin and d-penicillamine are two drugs that are known to bind excess cystine into a form that is more soluble than cystine alone and thus reduce the excessive urinary excretion of this amino acid. Since both tiopronin and d-penicillamine can have adverse side effects, patients on these regimens require follow-up to monitor the efficacy and tolerance of the medication. Other medications that reduce cystine excretion include mercaptopropionylglycine (MPG) and captopril. Although they are not as effective as tiopronin or d-penicillamine, MPG and captopril have fewer side effects.

If stones form despite the above therapeutic regimens, surgical intervention may be required. Surgical management of cystine stones may include dissolution of calculi by irrigation through a catheter, removal of cystine stones by lithotripsy or lithotomy, and renal transplantation. Catheter irrigation is a minimally invasive procedure in which catheters are placed into the ureters and the urinary tract is irrigated with a solution that dissolves the stones over a period of one week to several months. Lithotripsy is a medical procedure used to break a kidney stone into small pieces that can be passed in the urine. In extracorporeal shock wave lithotripsy, a shock wave produced outside the body is used to break up the stone and a catheter placed in the ureter facilitates passage of the stone fragments. In percutaneous nephrolithotripsy, an opening (port) is created by puncturing the kidney through the skin; a specialist then inserts instruments via this opening into the kidney to break up the stone and remove the debris. Lithotomy is the surgical removal of a (kidney) stone.

Prognosis

The prognosis of cystinuria is variable and depends on the level of renal function at the time of diagnosis and initiation of therapy, and the success of preventative measures and surgical management. It is known that males tend to have a more severe course and a higher mortality rate.

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ORGANIZATIONS

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WEBSITES

Cystinuria Support Network homepage. <http://www.cystinuria.com/>.

Dawn Cardeiro, MS, CGC

Cytogenetic mapping *see* **Gene mapping**

D

Dandy-Walker malformation

Definition

Dandy-Walker malformation is a congenital (present at birth) condition involving several abnormalities in the development of the brain. The malformation appears to result from destructive processes, such as inflammation or trauma, which block the circulation of cerebrospinal fluid (CSF) inside the head after the brain has been formed in the embryo.

Description

Dandy-Walker malformation was first described in 1914 by Drs. Dandy and Blackfan. The disorder typically includes the following abnormalities in brain structure:

- Absence or incomplete formation of the vermis, the middle portion of the cerebellum, which is the part of the human brain that lies behind the two cerebral hemispheres.
- Enlargement of the fourth ventricle, one of the human brain's four interconnected ventricles (inner cavities or chambers) that produce cerebrospinal fluid (CSF). In Dandy-Walker malformation, the CSF cannot circulate freely through the ventricles and the rest of the central nervous system (CNS), so it builds up inside the fourth ventricle and causes it to enlarge.
- Cysts (sacs) containing CSF are formed in the posterior fossa, which is a hollow at the back of the skull that covers the cerebellum.
- Absence or incomplete formation of the three foramina (small openings or holes) in the fourth ventricle.

In Dandy-Walker malformation, the CSF produced by the ventricles of the brain is not fully reabsorbed by the body; thus, the excess fluid accumulates in the fourth ventricle and the posterior fossa. As cysts in these areas grow, pressure from the fluid rises, producing a condition known as obstructive, or non-communicating, **hydrocephalus** (excess fluid on the brain). This type of hydrocephalus develops in 90% of children diagnosed with Dandy-Walker malformation. The size of the head may or may not be affected by pressure from the fluid.

Genetic profile

As of 2001, the genetic transmission of Dandy-Walker malformation is not fully understood because the disorder often occurs with other birth abnormalities including cleft palate, extra fingers (polydactyly) or fingers joined together (syndactyly), cataracts, and malformations of the face or heart. An abnormality in the central nervous system that often occurs together with Dandy-Walker malformation is agenesis (absence or failure to develop) of the corpus callosum, the thick band of nerve fibers that joins the two cerebral hemispheres. It is not yet clear whether these and other abnormalities in CNS development are determined by the same **gene** or whether they are inherited separately.

Dandy-Walker malformation appears to be transmitted in some families in an autosomal, or X-linked, recessive pattern, which means that both parents have one copy of the changed (mutated) gene but do not have the malformation. These families have a high risk of recurrence of the malformation. Families in which there has been inbreeding among close relatives also appear to transmit Dandy-Walker in an autosomal recessive pattern. Several **chromosomal abnormalities** have been associated with Dandy-Walker.

Demographics

Dandy-Walker malformation is a rare disorder. It is estimated to occur in about 3% of children with hydrocephalus, which occurs in 1–2 per 1,000 births. It appears to affect both sexes equally. While there is no known association with specific races or ethnic groups, recent genetic case studies of Dandy-Walker malformation include cases from Argentina, Poland, Germany, Brazil, Austria, and Japan.

KEY TERMS

Agenesis—Failure of an organ, tissue, or cell to develop or grow.

Congenital—Refers to a disorder which is present at birth.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Foramen—A small opening or hole in a body part or tissue. Dandy-Walker malformation is characterized by the absence or failure to develop the three foramina in the fourth ventricle of the brain.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Posterior fossa—Area at the base of the skull attached to the spinal cord.

Shunt—A small tube placed in a ventricle of the brain to direct cerebrospinal fluid away from the blockage into another part of the body.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

Ventricle—The fluid filled spaces in the center of the brain that hold cerebral spinal fluid.

Vermis—The central portion of the cerebellum, which divides the two hemispheres. It functions to monitor and control movement of the limbs, trunk, head, and eyes.

Signs and symptoms

Some signs of Dandy-Walker malformation may appear before birth. It is possible to detect hydrocephalus by ultrasound as early as 15-18 weeks after conception. A newborn with hydrocephalus may have difficulty breathing, dilated veins visible on the scalp, and rapid head growth. Infants with Dandy-Walker may be slow to develop motor (movement) skills, and may have abnormally large skulls as a result of the fluid pressure inside the head.

Older children with Dandy-Walker malformation may have symptoms associated with fluid pressure inside the head including vomiting, convulsions, and emotional irritability. If the cerebellum has been damaged, the child's sense of balance and coordination will be affected. About 20% of older children with Dandy-Walker have difficulty coordinating movements of the hands or feet (ataxia) or have involuntary jerking movements of the eyes (nystagmus). Developmental delays and mental retardation are more common. In some cases Dandy-Walker may be associated with an abnormal pituitary gland and delayed puberty. Other symptoms that sometimes appear in this group include unusually large head size, a bulge at the back of the head caused by fluid pressure in the posterior fossa, and abnormal breathing patterns.

Diagnosis

About 80% of children with Dandy-Walker malformation are diagnosed before the end of the first year, usually as a result of the signs of hydrocephalus. Following birth, the newborn's head circumference is measured to determine whether it has been enlarged by the development of cysts. As has already been mentioned, ultrasound screening before birth can detect some signs of hydrocephalus. Ultrasound screening is recommended if the family has a history of congenital neurologic abnormalities. **Genetic counseling** is recommended for parents who have already had a child with Dandy-Walker malformation as there is an increased risk that the malformation will reoccur in later pregnancies.

Imaging studies used to diagnose and monitor Dandy-Walker include:

- X rays of the skull to determine that the posterior fossa has been enlarged.
- CT scan or magnetic resonance imaging (MRI) tests to evaluate the size and shape of the fourth ventricle, the presence and size of the vermis, and the displacement of other parts of the brain by fluid pressure.
- Cranial ultrasound to evaluate the size of the ventricle or to assess the progression of hydrocephalus.
- Transillumination, a technique that shines a strong light through an organ or body part to assist in diagnosis. The posterior fossa may be transilluminated as part of the differential diagnosis of Dandy-Walker.

Treatment and management

Treatment of Dandy-Walker malformation is usually focused on managing hydrocephalus when it is present. Hydrocephalus cannot be cured, but it can be treated surgically by placing a shunt in the ventricles of the brain to reduce fluid pressure. The shunt carries some of the CSF into another part of the body where it can be reabsorbed.

Another important part of managing Dandy-Walker is treatment of conditions or abnormalities associated

with it—such as giving anticonvulsant medications for seizures or hormones to bring on puberty that has been delayed.

Prognosis

The prognosis for children with Dandy-Walker malformation is usually not encouraging because of the associated multiple abnormalities. Children with other congenital abnormalities occurring together with Dandy-Walker often do not survive. The affected person's chances of normal intellectual development depend on the severity of the malformation and the presence of other abnormalities.

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ORGANIZATIONS

Dandy-Walker Syndrome Network. 5030 142nd Path West, Apple Valley, MN 55124. (612) 423-4008.

Guardians of Hydrocephalus Research Foundation. 2618 Avenue Z, Brooklyn, NY 11235-2023. (718) 743-4473 or (800) 458-865. Fax: (718) 743-1171. ghrf2618@aol.com.

Hydrocephalus Association. 870 Market St. Suite 705, San Francisco, CA 94102. (415) 732-7040 or (888) 598-3789. (415) 732-7044. hydroassoc@aol.com. <http://neurosurgery.mgh.harvard.edu/ha>.

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Rebecca J. Frey, PhD

Dehydrogenase deficiency *see* **MCAD deficiency**

Deletion *see* **Chromosomal abnormalities**

Deletion 22q11 syndrome

Definition

Deletion 22q11 syndrome is a relatively common genetic disorder characterized by **congenital heart defects**, palate abnormalities, distinct facial features, immune problems, learning disabilities and other abnormalities. This syndrome is caused by a deletion of chromosomal material from the long arm of chromosome 22 (22q) that leads to a wide spectrum of effects.

Description

Deletion 22q11 syndrome is also known as velocardiofacial syndrome, DiGeorge syndrome, Sphrintzen syndrome, conotruncal anomaly face syndrome, and the CATCH-22 syndrome. Because of the wide variability in the features of this syndrome, medical professionals originally thought that deletion 22q11 syndrome was more than one syndrome and it was separately described by a number of physicians—Dr. DiGeorge, Dr. Sphrintzen, and others. Dr. DiGeorge described the more severe end of deletion 22q11 syndrome (infants with congenital heart defects, unusual facial features, and immune system abnormalities). The term velocardiofacial (VCF) syndrome was used for the milder end of deletion 22q11 syndrome. These individuals usually had palate anomalies, distinct facial features, and learning disabilities.

KEY TERMS

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Conotruncal heart abnormality—Congenital heart defects particularly involving the ventricular (lower chambers) outflow tracts of the heart includes subarterial ventricular septal defect, pulmonic valve atresia and stenosis, tetralogy of Fallot and truncus arteriosus.

Velo—Derived from the latin word *velum*, meaning palate and back of the throat.

Deletion 22q11 syndrome is an extremely variable syndrome. The main features are congenital heart defects, distinctive facial features, and palate (roof of the mouth) problems. Other problems include immune system abnormalities, thyroid problems, kidney abnormalities, and learning difficulties including mild developmental delay. Very rarely do individuals have all of the problems associated with this syndrome. Most individuals with deletion 22q11 syndrome have only a few of the associated features. Some individuals with 22q11 deletion syndrome are very mildly affected and others are more severely affected. The reason for the wide variability in this syndrome is not known.

Genetic profile

Deletion 22q11 syndrome is a genetic disorder caused by a deletion of chromosomal material from the long arm of chromosome 22. A series of genes are located in this region. Individuals with deletion 22q11 syndrome may have some or all of these genes deleted. This syndrome is sometimes called a microdeletion syndrome or a contiguous gene syndrome. Contiguous refers to the fact that these genes are arranged next to each other. The size of the deletion can be large or small, which may explain why some individuals with deletion 22q11 syndrome are more severely affected than others. The exact genes responsible for this syndrome are not known.

Deletion 22q11 syndrome is an autosomal dominant disorder. Genes always come in pairs and in an autosomal dominant disorder only one gene needs too be missing or altered for an individual to have the disorder. About 10–15% of the time, the deletion on the long arm of chromosome 22 that causes this syndrome is inherited from a parent. If a parent has deletion 22q11 syndrome, then there is a 50% chance that he or she will pass the deletion on to each of his or her children who will also be affected with 22q11 syndrome. For reasons that are not understood, it is possible for a parent with mild features of deletion 22q11 syndrome to have a child with severe features of the syndrome.

Although deletion 22q11 syndrome is an autosomal dominant disorder, over 85–90% of individuals with this disorder are the only individuals in their family with this disorder. When this is the case, the chromosome deletion that causes deletion 22q11 syndrome is called *de novo*. A *de novo* deletion is one that occurs for the first time in the affected individual. The causes of *de novo* chromosome deletions are not known. Parents of a child with deletion 22q11 syndrome due to a *de novo* deletion are very unlikely to have a second child with deletion 22q11 syndrome.

Demographics

The 22q11 deletion syndrome is one of the most common chromosomal deletion syndromes. It is estimated that approximately 1 in 2000 to 1 in 6000 individuals has a deletion of chromosome 22q11. Approximately 130,000 individuals in the United States have deletion 22q11 syndrome. Because of the extreme variability of this syndrome, it is possible that individuals with milder features are under diagnosed and the exact incidence of this disorder is not known. As more physicians become familiar with this syndrome, it is likely that more individuals will be correctly diagnosed.

Individuals with deletion 22q11 syndrome are diagnosed based upon physical findings. Of infants born with congenital heart defects, 5% will be found to have a deletion of chromosome 22q11. Of infants with a cleft palate, approximately 5–8% of them will be found to a have a 22q11 deletion.

Signs and symptoms

Deletion 22q11 syndrome is a multisystem disorder. It is also sometimes referred to as velocardiofacial syndrome. This name reflects the organ systems that are most commonly affected in deletion 22q11 syndrome. Velo is from the Latin *velum* which means “palate” and back of the throat, cardio refers to the heart, and facial refers to the distinctive facial features of individuals with deletion 22q11 syndrome. While it may seem unusual that these three separate areas are affected, a possible explanation lies in the early development of the embryo. Very early in development, the cells that will become the heart, face, and thyroid lie next to each other in a region called the neural crest. As the embryo continues to develop, these cells migrate, or move, to become organs (the heart, face, and palate). It is believed that the dele-

tion of chromosomal material from chromosome 22q causes a problem in the migration of these cells leading to the variability of features or problems seen in deletion 22q11 syndrome.

In addition to the heart, palate, and face, many other organ systems can also be affected including the kidneys, the immune system, the brain, the throat, the skeletal system, the skin, the genitourinary system, and the endocrine (hormone) system. It is not possible to cover every possible feature of deletion 22q11 syndrome but the following is an overview of the most common features.

The characteristic facial features seen in individuals with deletion 22q11 syndrome include a long face with narrow palpebral fissures (the opening for the eyes), a prominent nasal bridge (the arch of the nose between the eyes), a slightly bulbous nasal tip, a long nose, small ears with thick helical folds, and a small jaw. None of these features individually is abnormal but the combination of features is characteristically seen in individuals with deletion 22q11 syndrome. These features may not be present or as easily noticeable in African-American individuals with deletion 22q11 syndrome.

Approximately 70% of individuals with deletion 22q11 syndrome have palate abnormalities. These may include complete cleft palate (an opening of the bones and skin of the roof of the mouth) or submucous cleft palate (an opening of only the bones of the roof of the mouth covered by skin). Other individuals with deletion 22q11 syndrome have more subtle palate and throat abnormalities, including velopharyngeal insufficiency, a problem in the coordination between the tongue, palate, and throat muscles. All of these problems can lead to feeding problems in infancy and speech problems such as hypernasal speech.

Cardiac defects, or congenital heart defects, are some of the more serious symptoms of deletion 22q11 syndrome and affect about 75% of individuals with the syndrome. There is a wide range of cardiac defects seen in deletion 22q11 syndrome. Some are minor and may require no treatment, some are correctable by surgery, and others are invariably fatal. The most common heart defects seen in individuals with deletion 22q11 syndrome are truncus arteriosus, interrupted aortic arch, tetralogy of Fallot, ventricular septal defects (VSDs), pulmonary stenosis, and **patent ductus arteriosus**. Many of these heart defects are known as conotruncal heart defects. Conotruncal refers to the type of embryonic cells that were involved in the development of these regions of the heart.

Immune problems are another of the serious problems associated with this syndrome. Because of the underdevelopment of the thymus gland, individuals with deletion 22q11 syndrome can have reduced amounts of the cells necessary to fight infections—T cells. Because of this reduction in T cells, individuals with deletion 22q11 syndrome are more prone to getting infections and less able to fight them off. The degree of immune deficiency can be variable with some individuals having life threatening infections and others having much milder problems.

Growth problems may be seen in children with deletion 22q11 syndrome. Infants with deletion 22q11 syndrome are often diagnosed as having failure to thrive. This may be due to feeding problems due to their palate abnormalities but they can also have gastroesophageal reflux and vomiting problems. It also appears that individuals with deletion 22q11 syndrome have generalized growth problems. Most adult individuals with deletion 22q11 syndrome have short stature.

Individuals with deletion 22q11 syndrome may also have specific learning disabilities and possibly mild developmental delay. The learning disabilities are specific. Most individuals with learning disabilities have a discrepancy between their performance IQ score (higher) and their verbal IQ score (lower) that indicates a nonverbal learning disability. Simple IQ testing may not reveal this learning disability and it is important to evaluate the IQ score components separately. Individuals with deletion 22q11 syndrome seem to do better at verbal learning and do well in subjects such as reading. They have more trouble with abstract concepts such as math.

Individuals with deletion 22q11 syndrome are also at risk to develop psychological problems and mental illness. Deletion 22q11 syndrome has been associated with higher rates of bipolar affective disorder, manic-depressive illness, and schizoaffective disorder when compared to individuals who do not have deletion 22q11 syndrome. Other mood disorders, such as **depression**, also occur at a higher incidence in individuals with deletion 22q11 syndrome. Most of these disorders appear during adolescence or adulthood. Some individuals with deletion 22q11 syndrome are mildly mentally retarded. Others have learning disabilities and some are diagnosed as having attention deficit hyperactivity disorder.

Endocrine problems are also commonly seen. The endocrine system is the hormone-producing system of the body and is composed of glands such as the thyroid and parathyroid. Individuals with deletion 22q11 syndrome may be missing one or more of these glands or they have underactive glands. An underactive thyroid is called hypothyroidism and an underactive parathyroid is called hypoparathyroidism. Because the parathyroids help to regulate the level of calcium in the body, individuals with deletion 22q11 syndrome can also have problems with their calcium levels. Low levels of calcium can lead to seizures.

Individuals with deletion 22q11 syndrome may also have kidney problems such as a cystic kidney, missing (aplastic) kidney, or malformed kidney. They may also have limb differences such as such as extra fingers or ribs and problems with the vertebrae in the back that might lead to **scoliosis**.

Diagnosis

The diagnosis of deletion 22q11 syndrome is usually made by a physician familiar with the syndrome and based upon a physical examination of the individual and a review of his or her medical history. It is often made in infants after a heart problem is diagnosed. In children without significant heart problems, the possibility of a diagnosis may first be raised by preschool teachers or by other medical professionals such as plastic surgeons and speech therapists. These medical professionals may be seeing the child for one of the features of deletion 22q11 syndrome and may be the first ones to become suspicious about the diagnosis. In rare cases, the diagnosis is made in a parent after they have had an affected child.

While a diagnosis may be made based upon physical examination and medical history, the diagnosis can now be confirmed by a DNA test.

Sometimes the 22q11 deletion is large enough that it can be seen during a **karyotype** analysis. A karyotype is a microscopic analysis of an individual's **chromosomes**. However, many 22q11 deletions are too small to be seen by microscopic examination and another specific technique called fluorescent in situ hybridization testing, or FISH testing, can determine whether genetic material is missing. A FISH test will be positive (detect a deletion) in over 95% of individuals with deletion 22q11 syndrome. A negative FISH test for deletion 22q11 syndrome means that no genetic material is missing from the critical region on chromosome 22. Research testing on these individuals usually reveals that up to 5% of individuals with deletion 22q11 syndrome will have a smaller deletion that is not picked up by the routine FISH test.

Prenatal testing (testing during pregnancy) for deletion 22q11 syndrome is possible using the FISH test on a DNA sample obtained by chorionic villus sampling (CVS) or by **amniocentesis**. Chorionic villus sampling is a prenatal test that is usually done at 10–12 weeks of pregnancy and involves removing a small amount of tissue from the placenta. Amniocentesis is a prenatal test that is usually performed at 16–18 weeks of pregnancy and involves removing a small amount of the amniotic fluid that surrounds the fetus. DNA is obtained from these samples and tested to see if the deletion responsible for deletion 22q11 syndrome is present. While prenatal testing is possible, it is not routinely performed. Typically, the test is done only if there is a family history of deletion 22q11 syndrome or if a congenital heart defect has been seen on a sonogram (ultrasound).

A sonogram uses sound waves to provide an image of a fetus. During the second trimester of pregnancy, it becomes possible to evaluate the fetal heart. If a heart defect is detected, DNA testing may be offered to the parents (along with other tests) to determine the cause of the heart defect. Unfortunately, congenital heart defects are common and there are many other syndromes that also cause congenital heart defects.

Treatment and management

Because of the incredible variability seen in deletion 22q11 syndrome, there is no one plan of treatment for all affected individuals. The treatment and management of an individual with deletion 22q11 syndrome depends on his or her age and symptoms. Because deletion 22q11 syndrome is a multisystem disorder, it is important to have multiple evaluations. Individuals with deletion 22q11 syndrome may see geneticists, plastic surgeons, immunologists, cardiologists, rheumatologists, endocrinologists, ophthalmologists, neurosurgeons, pediatricians, audiologists, and specialists in feeding, speech, and child development.

It is important that all individuals with deletion 22q11 syndrome have a cardiac evaluation by a cardiologist. An evaluation may include special tests such as a chest x ray, electrocardiogram, and echocardiogram (ultrasound of the heart). Some cardiac defects do not require treatment and others may require surgery.

Because of the wide variety of cleft palate and velopharyngeal problems, all individuals with deletion 22q11 syndrome should be evaluated by a cleft palate team. Cleft palate teams may include a plastic surgeon, ENT (ear, nose, and throat) specialist, genetic counselor, and other staff. Because of the effect of cleft palate abnormalities on speech, all children with deletion 22q11 should have a speech evaluation and speech therapy if necessary. A referral to a feeding specialist may also be helpful if there is a cleft problem or other medical problem that interferes with feeding.

Because of the possibility and serious nature of immune problems, individuals with deletion 22q11 syndrome should have an immune evaluation. This can be done by an immunologist and usually requires blood tests to check immune function.

Individuals with deletion 22q11 syndrome should also have an endocrinology examination to check the

function of their thyroid, parathyroid, and pituitary glands. They may also see an endocrinologist if they are having growth problems.

Neurologists can help with issues such as seizures and other neurology problems. Psychiatrists can help with psychiatric illness and problems arising from having a chronic illness.

Individuals with deletion 22q11 syndrome should be seen by a geneticist to confirm the diagnosis and to discuss issues such as the **inheritance** of deletion 22q11 syndrome, the recurrence risks and the availability of prenatal diagnosis. Geneticists can also help arrange the necessary medical consults.

Prognosis

The prognosis for individuals with deletion 22q11 syndrome is highly dependant on the medical complications of the specific individual. Because this is such a variable syndrome, it is impossible to give one prognosis. The cardiac defects associated with deletion 22q11 syndrome are a major variable in determining prognosis. Those with serious heart defects have a guarded prognosis. Individuals with deletion 22q11 syndrome with minor or treatable cardiac defects have a good prognosis. Good medical care and treatment of problems allows most individuals with deletion 22q11 syndrome to have a normal life span.

While the physical features and medical complications of deletion 22q11 syndrome can affect prognosis, the degree of intellectual and psychological can also have an effect. Those individuals with normal IQ and no mental illness have a good prognosis. Those with learning disabilities can benefit from specific educational interventions. Individuals with developmental delay need more help but can do well in sheltered environments. Individuals with mental illness may or may not do well. Some individuals benefit from psychiatric counseling and medication.

The range of abilities among individuals with deletion 22q11 syndrome is very wide and the ultimate functioning of an individual is dependent on his or her abilities.

Resources

ORGANIZATIONS

National Institute on Deafness and Other Communication Disorders. 31 Center Dr., MSC 2320, Bethesda, MD 20814. <http://www.nidcd.nih.gov>.

Velo-Cardio-Facial Syndrome Educational Foundation. VCFS Educational Foundation, Inc., Upstate Medical University Hospital, 708 Jacobsen Hall (C.D.U.), 750 East Adams St., Syracuse, NY 13210.

Velo-Cardio-Facial Syndrome Research Institute. Albert Einstein College of Medicine, 3311 Bainbridge Ave., Bronx, NY 10467. (718) 430-2568. Fax: (718) 430-8778. rgoldber@aecom.yu.edu. <http://www.kumc.edu/gec/vcfhome.html>.

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McDonald-McGinn, Donna M., Beverly S. Emanuel, and Elaine H Zackai. "22q11 deletion syndrome." *Gene Clinics.* (Updated 15 Sept. 1999). <http://www.geneclinics.org/profiles/22q11deletion/index.html>.

National Institute on Deafness and Other Communication Disorders. <http://www.nidcd.nih.gov/health/pubs_vsl/velocario.htm>.

The VCFS Educational Foundation. <http://www.vcfsef.org/>.

Kathleen Fergus, MS, CGC

Delta storage pool disease *see* **Hermansky-Pudlak syndrome**

Dementia

Definition

Dementia is not a specific disorder or disease. It is a syndrome (group of symptoms) associated with a progressive loss of memory and other intellectual functions that is serious enough to interfere with the tasks of daily life. Dementia can occur to anyone at any age from an injury or oxygen deprivation, although it is most commonly associated with aging.

Description

The definition of dementia has become more inclusive over the past several decades. Whereas earlier descriptions of dementia emphasized memory loss, the last two editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R in 1987 and DSM-IV in 1994) define dementia as an overall decline in intellectual function, including difficulties with language, simple calculations, planning and judgment, and motor (muscular movement) skills as well as loss of memory. Although dementia is not caused by aging itself—most researchers regard it as resulting from injuries, infections, brain diseases, tumors, or other disorders—it is quite common in older people. Common estimates are that over 15% of people in North America over the age of 65 suffer from dementia, and 40% of people over 80. Surveys indicate that dementia is the condition most feared by older adults in the United States.

Dementia can be caused by nearly forty different diseases and conditions, ranging from dietary deficiencies and metabolic disorders to head injuries and inherited diseases. The possible causes of dementia can be categorized as follows:

- Primary dementia. These dementias are characterized by damage to or wasting away of the brain tissue itself. They include **Alzheimer disease** (AD), Pick's disease, and frontal lobe dementia (FLD).
- Multi-infarct dementia (MID). Sometimes called vascular dementia, this type is caused by blood clots in the small blood vessels of the brain. When the clots cut off the blood supply to the brain tissue, the brain cells are damaged and may die.
- Lewy body dementia. Lewy bodies are areas of injury found on damaged nerve cells in certain parts of the brain. They are associated with Alzheimer and **Parkinson disease**, but researchers do not yet know whether dementia with Lewy bodies is a distinct type of dementia or a variation of Alzheimer or Parkinson disease.
- Dementia related to **alcoholism** or exposure to heavy metals (arsenic, antimony, bismuth).
- Dementia related to infectious diseases. These infections may be caused by viruses (HIV, viral encephalitis); spirochetes (Lyme disease, syphilis); or prions (Creutzfeldt-Jakob disease).
- Dementia related to abnormalities in the structure of the brain. These may include a buildup of spinal fluid in the brain (**hydrocephalus**); tumors; or blood collecting beneath the membrane that covers the brain (subdural hematoma).

Dementia may also be associated with **depression**, low levels of thyroid hormone, or niacin (vitamin B_{12}) deficiency. Dementia related to these conditions is often reversible.

Genetic profile

Genetic factors play a role in several types of dementia, but the importance of these factors in the development of the dementia varies considerably. Alzheimer disease (AD) is known, for example, to have an autosomal (non-sex-related) dominant pattern in most early-onset cases as well as in some late-onset cases, and to show different degrees of penetrance (frequency of expression) in late-life cases. Moreover, researchers have not yet discovered how the genes associated with dementia interact with other risk factors to produce or trigger the dementia. One non-genetic risk factor presently being investigated is toxic substances in the environment.

Early-onset Alzheimer disease

In early-onset AD, which accounts for 2–7% of cases of AD, the symptoms develop before age 60. It is usually caused by an inherited genetic mutation. Early-onset AD is also associated with **Down syndrome**, in that persons with trisomy 21 (three forms of human chromosome 21 instead of a pair) often develop early-onset AD.

Late-onset Alzheimer disease

Recent research indicates that late-onset Alzheimer disease is a polygenic disorder; that is, its development is influenced by more than one **gene**. It has been known since 1993 that a specific form of a gene for apolipoprotein E (APOE) on human chromosome 19 is a genetic risk factor for late-onset AD. In 1998 researchers at the University of Pittsburgh reported on another gene that controls the production of bleomycin hydrolase (BH) as a second genetic risk factor that acts independently of the APOE gene. In December 2000, three separate research studies reported that a gene on chromosome 10 that may affect the processing of amyloid-beta protein is also involved in the development of late-onset AD.

Multi-infarct dementia (MID)

While the chief risk factors for MID are high blood pressure, advanced age, and male sex, there is an inherited form of MID called CADASIL, which stands for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CADASIL can cause psychiatric disturbances and severe headaches as well as dementia.

Frontal lobe dementias

Researchers think that between 25% and 50% of cases of frontal lobe dementia involve genetic factors. Pick's dementia appears to have a much smaller genetic component than FLD. It is not yet known what other risk factors combine with inherited traits to influence the development of frontal lobe dementias.

Familial British dementia (FBD)

FBD is a rare autosomal dominant disorder that was first reported in the 1940s in a large British family extending over nine generations. FBD resembles Alzheimer in that the patient develops a progressive dementia related to amyloid deposits in the brain. In 1999 a mutated gene that produces the amyloid responsible for FBD was discovered on human chromosome 13. Studies of this mutation may yield further clues to the development of Alzheimer disease as well as FBD itself.

KEY TERMS

Age-associated memory impairment (AAMI)—A condition in which an older person suffers some memory loss and takes longer to learn new information. AAMI is distinguished from dementia in that it is not progressive and does not represent a serious decline from the person's previous level of functioning.

Agnosia—Loss of the ability to recognize objects by use of the physical senses.

Amyloid—A waxy translucent substance composed mostly of protein, that forms plaques (abnormal deposits) in the brain.

Aphasia—Loss of previously acquired ability to speak, or to understand written or spoken language.

Apraxia—Impairment of the ability to make purposeful movements, but not paralysis or loss of sensation.

Creutzfeldt-Jakob disease—A degenerative disease of the central nervous system caused by a prion, or "slow virus."

Delirium—A disturbance of consciousness marked by confusion, difficulty paying attention, delusions, hallucinations, or restlessness. It can be distinguished from dementia by its relatively sudden onset and variation in the severity of the symptoms.

Hematoma—An accumulation of blood, often clotted, in a body tissue or organ, usually caused by a break or tear in a blood vessel.

Huntington disease—A midlife-onset inherited disorder characterized by progressive dementia and loss of control over voluntary movements. It is sometimes called Huntington's chorea.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Lewy bodies—Areas of injury found on damaged nerve cells in certain parts of the brain associated with dementia.

Multi-infarct dementia—Dementia caused by damage to brain tissue resulting from a series of blood clots or clogs in the blood vessels. It is also called vascular dementia.

Parkinson disease—A disease of the nervous system most common in people over 60, characterized by a shuffling gait, trembling of the fingers and hands, and muscle stiffness. It may be related in some way to Lewy body dementia.

Pick's disease—A rare type of primary dementia that affects the frontal lobes of the brain. It is characterized by a progressive loss of social skills, language, and memory, leading to personality changes and sometimes loss of moral judgment.

Pseudodementia—A term for a depression with symptoms resembling those of dementia. The term dementia of depression is now preferred.

Creutzfeldt-Jakob disease

Although Creutzfeldt-Jakob disease is caused by a prion, researchers think that 5–15% of cases may have a genetic component.

Demographics

The demographic distribution of dementia varies somewhat according to its cause. Moreover, recent research indicates that dementia in many patients has overlapping causes, so that it is not always easy to assess the true rates of occurrence of the different types. For example, AD and MID are found together in about 15–20% of cases.

Alzheimer disease

AD is by far the most common cause of dementia in the elderly, accounting for 60–80% of cases. It is estimated that 4 million adults in the United States suffer from AD. The disease strikes women more often than men, but researchers don't know yet whether the sex ratio simply reflects the fact that women tend to live longer than men, or whether female sex is itself a risk factor for AD. One well-known long-term study of Alzheimer's in women is the Nun Study, begun in 1986 and presently conducted at the University of Kentucky.

Multi-infarct dementia

MID is responsible for between 15% and 20% of cases of dementia (not counting cases in which it coexists with AD). Unlike AD, MID is more common in men than in women. Diabetes, high blood pressure, a history of smoking, and heart disease are all risk factors for MID. Researchers in Sweden have suggested that MID is underdiagnosed, and may coexist with other dementias more frequently than is presently recognized.

Dementia with Lewy bodies

Dementia with Lewy bodies is now thought to be the second most common form of dementia after Alzheimer disease. But because researchers do not completely understand the relationship between Lewy bodies, AD, and Parkinson disease, the demographic distribution of this type of dementia is also unclear.

Other dementias

FLD, Pick's disease, **Huntington disease**, Parkinson disease, HIV infection, alcoholism, head trauma, etc. account for about 10% of all cases of dementia. In FLD and Pick's dementia, women appear to be affected slightly more often than men.

Signs and symptoms

DSM-IV specifies that certain criteria must be met for a patient to be diagnosed with dementia. One criterion is significant weakening of the patient's memory with regard to learning new information as well as recalling previously learned information. In addition, the patient must be found to have one or more of the following disturbances:

- Aphasia. Aphasia refers to loss of language function. A person with dementia may use vague words like "it" or "thing" a lot because they can't recall the exact name of an object; they may echo what other people say, or repeat a word or phrase over and over. People in the later stages of dementia may stop speaking at all.
- Apraxia. Apraxia refers to loss of the ability to perform intentional movements even though the person is not paralyzed, has not lost their sense of touch, and knows what they are trying to do. For example, patients with apraxia may stop brushing their teeth, or have trouble tying their shoelaces.
- Agnosia. Agnosia refers to loss of the ability to recognize objects even though the person's sight and sense of touch are normal. People with severe agnosia may fail to recognize family members or their own face reflected in a mirror.
- Problems with abstract thinking and complex behavior. This criterion refers to the loss of the ability to make plans, carry out the steps of a task in the proper order, make appropriate decisions, evaluate situations, show good judgment, etc. For example, a patient might light a stove burner under a saucepan before putting food or water in the pan, or be unable to record checks and balance his or her checkbook.

DSM-IV also specifies that these disturbances must be severe enough to cause problems in the person's daily life, and that they must represent a decline from a previously higher level of functioning.

The following sections will focus on the signs and symptoms that are used to differentiate among the various types of dementia during a diagnostic evaluation.

Alzheimer disease

Dementia related to AD often progresses slowly; it may be accompanied by irritability, wide mood swings, and personality changes in the early stage. In second-stage AD, the patient typically gets lost easily, is completely disoriented with regard to time and space, and may become angry, uncooperative, or aggressive. In final-stage AD, the patient is completely bedridden, has lost control over bowel and bladder functions, and may be unable to swallow or eat. The risk of seizures increases as the patient progresses from early to end-stage Alzheimer disease. Death usually results from an infection or malnutrition.

Multi-infarct dementia

In MID, the symptoms are more likely to occur after age 70. In the early stages, the patient retains his or her personality more fully than a patient with AD. Another distinctive feature of this type of dementia is that it often progresses in a stepwise fashion; that is, the patient shows rapid changes in functioning, then remains at a plateau for awhile rather than showing a continuous decline. The symptoms of MID may also have a "patchy" quality; that is, some of the patient's mental functions may be severely affected while others are relatively undamaged. Other symptoms of MID include exaggerated reflexes, an abnormal gait (manner of walking), loss of bladder or bowel control, and inappropriate laughing or crying.

Dementia with Lewy bodies

This type of dementia may combine some features of AD, such as severe memory loss and confusion, with certain symptoms associated with Parkinson disease, including stiff muscles, a shuffling gait, and trembling or shaking of the hands. Visual hallucinations may be one of the first symptoms of dementia with Lewy bodies.

Frontal lobe dementias

The frontal lobe dementias are gradual in onset. Pick's dementia is most likely to develop in persons between 40 and 60, while FLD typically begins before the age of 65. The first symptoms of the frontal lobe dementias often include socially inappropriate behavior (rude remarks, sexual acting-out, lack of personal

hygiene, etc.). Patients are also often obsessed with eating and may put non-food items in their mouths as well as making frequent sucking or smacking noises. In the later stages of frontal lobe dementia or Pick's disease, the patient may develop muscle weakness, twitching, and delusions or hallucinations.

Creutzfeldt-Jakob disease

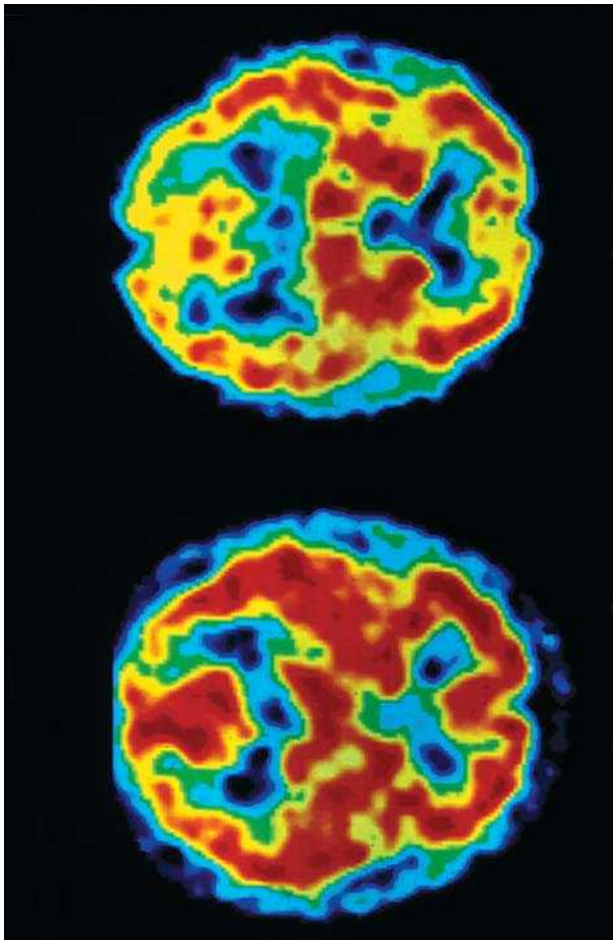
The dementia associated with Creutzfeldt-Jakob disease occurs most often in persons between 40 and 60. It is typically preceded by a period of several weeks in which the patient complains of unusual tiredness, anxiety, loss of appetite, or difficulty concentrating. This type of dementia also usually progresses much more rapidly than other dementias, usually over a span of a few months.

Diagnosis

In some cases, a patient's primary physician may be able to diagnose the dementia; in many instances, however, the patient will be referred to a neurologist or a specialist in geriatric medicine. The differential diagnosis of dementia is complicated because of the number of possible causes; because more than one cause may be present; and because dementia can coexist with other conditions such as depression and delirium. Delirium is a temporary disturbance of consciousness marked by confusion, restlessness, inability to focus one's attention, hallucinations, or delusions. In elderly people, delirium is frequently a side effect of surgery, medications, infectious illnesses, or dehydration. Delirium can be distinguished from dementia by the fact that delirium usually comes on fairly suddenly (in a few hours or days) and may vary in severity—it is often worse at night. Dementia develops much more slowly, over a period of months or years, and the patient's symptoms are relatively stable. It is possible for a person to have delirium and dementia at the same time. Another significant diagnostic distinction in elderly patients is the distinction between dementia and age-associated memory impairment (AAMI). Older people with AAMI have a mild degree of memory loss; they do not learn new information as quickly as younger people, and they may take longer to recall a certain fact or to balance their checkbook. But they do not suffer the degree of memory impairment that characterizes dementia, and they do not get progressively worse.

Patient history

The doctor will begin by taking a full history, including the patient's occupation and educational level as well as medical history. The occupational and educational history allows the examiner to make a more accurate assessment of the extent of the patient's memory loss and other evidence of intellectual decline. In some cases the occupational history may indicate exposure to heavy metals or other toxins. A complete medical history allows the doctor to assess possibilities such as delirium, depression, alcohol-related dementia, dementia related to head injury, or dementia caused by infection. It is particularly important for the doctor to have a list of all the patient's medications, including over-the-counter preparations, because of the possibility that the patient's symptoms are related to side effects.



Colored positron emission of dementia in a patient with AIDS. *(Photo Researchers, Inc.)*

Mental status examination

A mental status examination (MSE) evaluates the patient's ability to communicate, follow instructions, recall information, perform simple tasks involving movement and coordination, as well as his or her emotional state and general sense of space and time. The MSE includes the doctor's informal evaluation of the patient's

appearance, vocal tone, facial expressions, posture, and gait as well as formal questions or instructions. A common form that has been used since 1975 is the so-called Folstein Mini-Mental Status Examination, or MMSE. Questions that are relevant to diagnosing dementia include asking the patient to count backward from 100 by 7s, to make change, to name the current President, to repeat a short phrase after the examiner (e.g., "no ifs, ands, or buts"), to draw a clock face or geometric figure, and to follow a set of instructions involving movement (e.g., "Show me how to throw a ball" or "Fold this piece of paper and place it under the lamp on the bookshelf."). The examiner may test the patient's abstract reasoning ability by asking him or her to explain a familiar proverb (e.g. "People who live in glass houses shouldn't throw stones") or test the patient's judgment by asking about a problem with a common-sense solution, such as what one does when a prescription runs out.

Neurological examination

A neurological examination includes an evaluation of the patient's cranial nerves and reflexes. The cranial nerves govern the ability to speak as well as sight, hearing, taste, and smell. The patient will be asked to stick out the tongue, follow the examiner's finger with the eyes, raise the eyebrows, etc. The patient is also asked to perform certain actions (e.g., touching the nose with the eyes closed) that test coordination and spatial orientation. The doctor will usually touch or tap certain areas of the body, such as the knee or the sole of the foot, to test the patient's reflexes. Failure to respond to the touch or tap may indicate damage to certain parts of the brain.

Laboratory tests

Blood and urine samples are collected in order to rule out such conditions as thyroid deficiency, niacin (vitamin B_{12}) deficiency, heavy metal poisoning, liver disease, HIV infection, syphilis, anemia, medication reactions, or kidney failure. A lumbar puncture (spinal tap) may be done to rule out neurosyphilis.

Diagnostic imaging

The patient may be given a CT (computed tomography) scan or MRI (magnetic resonance imaging) to detect evidence of strokes, disintegration of the brain tissue in certain areas, blood clots or tumors, a buildup of spinal fluid, or bleeding into the brain tissue. PET (positron-emission tomography) or SPECT (single-emission computed tomography) imaging is not used routinely to diagnose dementia, but may be used to rule out Alzheimer disease or frontal lobe degeneration if a patient's CT scan or MRI is unrevealing.

Treatment and management

Reversible and responsive dementias

Some types of dementia are reversible, and a few types respond to specific treatments related to their causes. Dementia related to dietary deficiencies or metabolic disorders is treated with the appropriate vitamins or thyroid medication. Dementia related to HIV infection often responds well to zidovudine (Retrovir), a drug given to prevent the AIDS virus from replicating. Multi-infarct dementia is usually treated by controlling the patient's blood pressure and/or diabetes; while treatments for these disorders cannot undo damage already caused to brain tissue, they can slow the progress of the dementia. Patients with alcohol-related dementia often improve over the long term if they are able to stop drinking. Dementias related to head injuries, hydrocephalus, and tumors are treated by surgery.

It is important to evaluate and treat elderly patients for depression, because the symptoms of depression in older people often mimic dementia. This condition is sometimes called pseudodementia. In addition, patients who suffer from both depression and dementia often show some improvement in intellectual functioning when the depression is treated.

Irreversible dementias

As of 2001, there are no medications or surgical techniques that can cure Alzheimer disease, the frontal lobe dementias, MID, or dementia with Lewy bodies. There are also no "magic bullets" that can slow or stop the progression of these dementias. Patients may be given medications to ease the depression, anxiety, sleep disturbances, and similar symptoms that accompany dementia, but most physicians prescribe relatively mild dosages in order to minimize the troublesome side effects of these drugs. Dementia with Lewy bodies appears to respond better to treatment with the newer antipsychotic medications than to treatment with such older drugs as haloperidol (Haldol).

Patients in the early stages of dementia can often remain at home with some help from family members or other caregivers, especially if the house or apartment can be fitted with safety features (handrails, good lighting, locks for cabinets containing potentially dangerous products, nonslip treads on stairs, etc.). Patients in the later stages of dementia, however, usually require skilled care in a nursing home or hospital.

Prognosis

The prognosis for reversible dementia related to nutritional or thyroid problems is usually good once the

cause has been identified and treated. The prognoses for dementias related to alcoholism or HIV infection depend on the patient's age and the severity of the underlying disorder.

The prognosis for the irreversible dementias is gradual deterioration of the patient's functioning ending in death. The length of time varies somewhat. Patients with Alzheimer disease may live from two to 20 years with the disease, with an average of seven years. Patients with frontal lobe dementia or Pick's disease live on average between five and 10 years after diagnosis. The course of Creutzfeldt-Jakob disease is much more rapid, with patients living between five and 12 months after diagnosis.

Resources

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Morris, Virginia. *How to Care for Aging Parents.* New York: Workman Publishing, 1996. A good source of information about caring for someone with dementia as well as information about dementia itself.

ORGANIZATIONS

Alzheimer's Association. 919 North Michigan Ave., Suite 1000, Chicago, IL 60611-1676. (800) 272-3900.

Alzheimer's Disease International. 45/46 Lower Marsh, London, SE1 7RG. UK (+44 20) 7620 3011. adi@alz.co.uk. <http://www.alz.co.uk.>.

National Institute of Mental Health. 6001 Executive Blvd., Rm. 8184, MSC 9663, Bethesda, MD 20892-9663. (301) 443-4513. Fax: (301) 443-4279. <http://www.nimh.nih.gov/publicat/index.cfm>.

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Institute on Aging Information Center. PO Box 8057, Gaithersburg, MD 20898. (800) 222-2225 or (301) 496-1752.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Alzheimer's Disease Education and Referral (ADEAR). <http://www.alzheimers.org>.

National Institute of Mental Health (NIMH). <http://www.nimh.nih.gov>.

National Institute of Neurological Disorders and Stroke (NINDS). <http://www.ninds.nih.gov>.

National Institute on Aging (NIA). <http://www.nih.gov/nia>.

The Nun Study. <http://www.coa.uky.edu/nunnet>.

Rebecca J. Frey, PhD

Dentatorubral-pallidoluysian atrophy

Definition

Dentatorubral-pallidoluysian atrophy (DRPLA) is a disorder of ataxia (loss of balance), choreoathetosis (involuntary rapid, irregular, jerky movements or slow, writhing movements that flow into one another), and **dementia** (inability to clearly think; confusion, poor judgement; failure to recognize people, places, and things; personality changes) in adults, and ataxia, myoclonus (involuntary spasms of a muscle or muscle group), **epilepsy** (seizures), and loss of intellectual function (mental retardation) in children.

Description

DRPLA has also been referred to as Haw River syndrome and Natito-Oyanagi disease. The typical age of onset of DRPLA is 30, but it can present in people as young as one year of age and as late as 62 years of age, with differences in presentation between children and adults. In patients under the age of 20, DRPLA presents as seizures, ataxia, myoclonus, as well as progressive (worsening) mental deterioration. In patients over the age of 20, DRPLA is suspected when a person develops ataxia, choreoathetosis, dementia, and psychiatric disturbances (delusions, hallucinations). A positive family history (a relative with similar symptoms or one already diagnosed) confirms the diagnosis. DRPLA is sometimes initially thought to be **Huntington disease**.

A possible diagnosis of DRPLA can be devastating for a family to experience—their once healthy child, or young adult, will begin to have seizures, involuntary movements, loss of control over voluntary movement, and delusions—perhaps no longer being able to identify family members. Diagnosing DRPLA is complicated and requires a knowledgeable phyisician with expertise in both neurology and genetics. Usually an individual diagnosed with DRPLA already has a parent with the disease,

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid which surrounds a developing baby during pregnancy.

Anticipation—Increasing severity in disease with earlier ages of onset, in successive generations; a condition that begins at a younger age and is more severe with each generation

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Choreoathetosis—Involuntary rapid, irregular, jerky movements or slow, writhing movements that flow into one another.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

DNA repeats—A three letter section of DNA, called a triplet, which is normally repeated several times in a row. Too many repeats often cause the gene to not function properly, resulting in disease.

DRPLA—Dentatorubral-pallidoluysian atrophy; also called Haw River syndrome and Natito-Oyanagi disease. DRPLA is a disorder of ataxia, choreoathetosis, and dementia in adults, and ataxia, myoclonus, epilepsy, and mental retardation in children.

Epilepsy—A seizure disorder.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

however, if the disorder was not diagnosed properly, or the parent died prior to the onset of symptoms, or the parent has very late onset of the disease, there may not be a documented family history of DRPLA.

Genetic profile

DRPLA is an autosomal dominant condition which means that both males and females are equally likely to have the disease, and an individual with the variant **gene** has a 50/50 chance to pass the condition to any child. The DRPLA gene is located on chromosome number 12 and has a section of **DNA** where the DNA alphabet is repeated in triplets, called CAG repeats. Normally a person has 6 to 35 CAG repeats in the DRPLA gene. In patients with DRPLA, there are 49 to 88 repeats which causes the gene's protein product, Atrophin 1, to be toxic to cells. Although scientists do not understand the exact mechanism, the number of repeats expands when the gene is transmitted from parent to child. The size of the repeat transmitted to the next generation depends upon the size of the parent's repeat and the sex of the transmitting parent.

There is an inverse correlation between the age of onset and the size of the expanded CAG repeats. In other words, the younger the age of onset, the larger the number of CAG repeats:

- Onset before age 21—repeat range of 63–69 (average of 68).
- Onset from 21–40 years—repeat range of 61–69 (average of 64).
- Onset after 40 years—repeat range of 54–63 (average of 63). Although there is significant overlap, the inverse correlation exists.

DRPLA as well as other genetic conditions, exhibits a phenomenon known as anticipation. Anticipation means that the disease increases in severity and presents at a younger age of onset with each successive generation. For example, when the CAG repeat is inherited from the father, DRPLA can manifest itself 28 years earlier than the father began having symptoms, while if transmitted from the mother, DRPLA can present 15 years earlier than the previous generation.

Demographics

DRPLA has been reported to occur most often in the Japanese population, although it has been described in other ethnic groups including those in Europe and North America. The prevalence of DRPLA in the Japanese population is estimated to be 2–7 in 1,000,000, which is similar to the prevalence of Huntington disease in this population. A CAG repeat size of 17 or higher (usually 20–35) is more common in healthy Japanese individuals than Caucasians, which may explain why DRPLA is more common in the Japanese. In other words, a larger repeat size in a parent increases the possibility that the DNA will become unstable and expand when transmitted to the next generation. Even though DRPLA is rare in the United States, a large African-American family in North Carolina has DRPLA, where the condition is also called the Haw River syndrome.

Signs and symptoms

The cardinal features of DRPLA are involuntary movements (usually in the face, neck, tongue and hands) and dementia (inability to clearly think; confusion; poor judgement; failure to recognize people, places, and things; personality changes) regardless of the age of onset. A history of ataxia, epilepsy, and mental retardation in children, combined with a positive family history, are often the presenting signs of this condition in an individual under 20 years of age. Seizures are always present in patients under 20, but are not as common in patients age 20–40, and rarely seen in patients with onset after 40. Adult onset DRPLA (after 20) presents with ataxia, choreoathetosis, dementia, and psychiatric disturbances.

Diagnosis

A diagnosis of DRPLA exists when there is a positive family history of the disease, characteristic clinical findings, and DNA testing that reveals an expansion in the CAG repeat of the DRPLA gene. **Genetic testing** to examine the CAG repeats in the DRPLA gene can be performed from a small blood sample. A few reports have described DRPLA as sporadic (occuring by chance) in some families. Upon closer examination, the asymptomatic fathers had a mildly expanded CAG repeat size. Therefore, it is always important to evaluate both parents of an affected individual even if they appear to have no symptoms of DRPLA. Testing of asymptomatic children is not appropriate since it takes away the child's right to want to know, or not know this information, raises the possibility of stigmatization (labeling someone a certain way and making assumptions about them) within a family, as well as the threat of educational and employment discrimination. Children *with* symptoms, however, usually benefit from having a diagnosis established.

For pregnancies at 50% risk, prenatal diagnosis is available via either CVS (chorionic villus sampling) or **amniocentesis**. CVS is a biopsy of the placenta performed in the first trimester of pregnancy under ultrasound guidance. Ultrasound is the use of sound waves to visualize the developing pregnancy. The genetic makeup of the placenta is identical to the fetus (developing baby) and therefore the DRPLA gene can be studied from this tissue. There is approximately a 1 in 100 chance for miscarriage with CVS. Amniocentesis is a procedure done under ultrasound guidance where a long thin needle is inserted into the mother's abdomen, into the uterus, to withdraw a couple of tablespoons of amniotic fluid (fluid surrounding the developing baby) to study. The DRPLA gene can be studied using cells from the amniotic fluid. Other genetic tests, such as a chromosome analysis, may also be performed on either a CVS or amniocentesis. A small risk of miscarriage (1 in 200 to 1 in 400) is associated with amniocentesis.

Treatment and management

There is currently no cure for DRPLA; treatment is supportive. Epilepsy is treated with anti-seizure medication.

Prognosis

Patients with DRPLA have progressive disease, which means symptoms become worse over time.

Resources

WEBSITES

International Network of Ataxia Friends (INTERNAF). <http://www.internaf.org>.

National Ataxia Foundation. <http://www.ataxia.org>.

WE MOVE (Worldwide Education and Awareness for Movement Disorders). <http://www.wemove.org>.

Catherine L. Tesla, MS, CGC

Deoxyribonucleic acid *see* **DNA**

Depression

Definition

Depression is the general name for a family of illnesses known as depressive disorders. Depression is an illness that affects not only the mood and thoughts, but also the physical functions of affected individuals. Depressive disorders usually result from a combination of genetic, environmental, and psychological factors.

Description

Everyone feels sadness, grief, or despair at some point in their lives. However, unlike these normal, transient emotional states, a depressive disorder is not a temporary bout of "feeling down" but rather a serious disease that should be recognized and treated as a medical condition. Without treatment, a depressive disorder can persist and its symptoms can go on for weeks, months, or years. The three most common types of depression are dysthymia or dysthymic disorder, major depression, and **bipolar disorder**.

Depression is quite widespread and one of the leading causes of disability in the world. Commonly recognized symptoms of all types of depressive disorders are recurring feelings of sadness and guilt, changes in sleeping patterns such as insomnia or oversleeping, changes in appetite, decreased mental and physical energy, unusual irritability, the inability to enjoy once-favored activities, difficulty in working, and thoughts of death or suicide. If only these "down" symptoms are experienced, the individual may suffer from a unipolar depressive disorder such as dysthymia or major depression. If the depressed periods alternate with extreme "up" periods, the individual may have a bipolar disorder.

Dysthymia is a relatively mild depressive disorder that is characterized by the presence of two or more of the symptoms listed above. The symptoms are not severe enough to disable the affected individual, but are long-term (chronic), and may last for several years. Dysthymia is a compound word originating in Greek that means ill, or bad, (dys-) soul, mind, or spirit (thymia). Individuals affected with dysthymia often also experience episodes of major depression at some point in their lives.

In major depression, the affected individual has five or more symptoms and experiences one or more prolonged episodes of depression that last longer than two weeks. These episodes disrupt the ability of the affected individual to the point that the person is unable to function. Individuals experiencing an episode of major depression often entertain suicidal thoughts, the presence of which contribute to this disorder being quite serious. Major depression should not be confused with a *grief reaction* such as that associated with the death of a loved one. Some individuals affected by major depression may experience only a single bout of disabling depression in their lifetimes. More commonly, affected individuals experience recurrent disabling episodes throughout their lives.

Bipolar disorder, formerly called manic depression or manic-depressive illness, is not nearly as common as major depression and dysthymia. Bipolar disorder is associated with alternating periods of extreme excitement (mania) and periods of extreme sadness (depression). The rate of the transition between cycles is usually gradual, but the mood swings may also be severe and dramatically rapid. When in the depressive state, the bipolar disorder affected individual may show any or all of the common symptoms of depression. In the manic state, the bipolar disorder affected individual may feel restless and unnaturally elated, have an overabundance of confidence and energy, and be very talkative. Mania can distort social behavior and judgment, causing the affected individual to take excessive risks and perhaps make imprudent decisions that can have humiliating or damaging consequences. Without medical treatment, bipolar disorder may progress into psychosis.

Depressive disorders are believed to be related to imbalances in brain chemistry, particularly in relation to the chemicals that carry signals between brain cells (neurotransmitters) as well as the hormones released by parts of the brain. Serotonin and neuroepinephrine are two important neurotransmitters. Disruption of the brain's circuits in areas involved with emotions, appetite, sexual drive, and sleep is a likely cause of the dysfunctions associated with depressive disorders. Thus, some of the newest treatments for depression are drugs that are known to have an effect on brain chemistry.

Genetic profile

Depression is known to be genetically linked because it often runs in families and has been studied in identical twins, but the specific gene markers for depression remain elusive. As of early 2000, the National Institutes of Mental Health has begun enrolling patients in what will become the largest clinical psychiatric genetic study ever attempted to investigate how recurrent depression is transmitted across generations. This study is primarily focused on major depression and dysthymia.

In familial cases of bipolar disorder, the most widely implicated genetic regions are those of chromosome 18 and chromosome 21. However, other researchers have mapped bipolar disorder to **chromosomes** 11p, Xq28, 6p, and many others. From this evidence, it is possible that bipolar disorder is a multi-gene (polygenic) trait requiring a combination of 3 or more genes on separate chromosomes for the condition to be expressed. Further research is also ongoing to determine the genetic marker, or markers, for bipolar disorder.

It is understood that there are also many non-genetic factors that cause depression, including stressful environmental conditions, certain illnesses, and precipitating conditions such as the loss of a close relationship. Alcohol abuse and the use of sedatives, barbiturates, narcotics, or other drugs can cause depression due to their effect on brain chemistry.

Demographics

It is estimated that the likelihood of experiencing an episode of major depression during one's lifetime is 5 percent. Approximately 9.5% of the American population, or 19 million people, are affected by depression in any given year. Depression occurs worldwide, but more Americans are diagnosed with depression than inhabitants of any other country. These lower occurrences of diagnosis in other parts of the world might indicate a higher incidence of depression in Americans than in all other peoples, but it may also be the result of the stigma, or shame, often associated with the diagnosis of a psychological disorder. Depression is not generally linked to any particular race of people.

In the United States, women experience depression at a rate that is almost twice that of men. This may be partially explained by the greater willingness of women to seek psychological treatment, but this does not explain the entire discrepancy. Many physical events specific to women, such as menstruation, pregnancy, miscarriage, the post partum period, and menopause are recognized as factors contributing to depression in women. Women in the United States may face environmental stresses with a higher frequency than men. Most single parent households are headed by women; women still provide the majority of child and elder care, even in two-income families; and women are generally paid less than men, so financial concerns may be greater.

Particular demographic problems associated with depression are depression in the elderly and depression in children and adolescents. A common belief is that depression is normal in elderly people. This is not the case, although increasing age and the absence of interpersonal relationships are associated with higher rates of depression. Because of this misconception, depressive disorders in the elderly population often go undiagnosed and untreated. Similarly, many parents often ignore the symptoms of a depressive disorder in their children, assuming that these symptoms are merely a phase that the child will later outgrow.

Signs and symptoms

Individuals affected with depressive disorders display a wide range of symptoms. These symptoms vary in severity from person to person and vary over time in a single affected individual.

Symptoms that characterize a depressive state are: feelings of hopelessness, guilt, or worthlessness; a persistent sad or anxious mood; restlessness or irritability; a loss of interest in activities that were once considered pleasurable; difficulty concentrating, remembering, or making decisions; sleep disorders, including insomnia, early morning awakening, and/or oversleeping; constant fatigue; eating disorders, including weight loss or overeating; suicidal thoughts and/or tendencies; and persistent physical symptoms that do not respond to the normal treatments of these symptoms, such as headaches, digestive problems, and chronic pain.

KEY TERMS

Bipolar disorder—Formerly called "manic depression," this psychological disorder is characterized by periods of mania followed by periods of depression.

Cognitive/behavioral therapies—Psychological counseling that focuses on changing the behavior of the patient.

Dysthymia—A psychological condition of chronic depression that is not disabling, but prevents the sufferer from functioning at his or her full capacity.

Electroconvulsive therapy—A psychological treatment in which a series of controlled electrical impulses are delivered to the brain in order to induce a seizure within the brain.

Grief reaction—The normal depression felt after a traumatic major life occurrence such as the loss of a loved one.

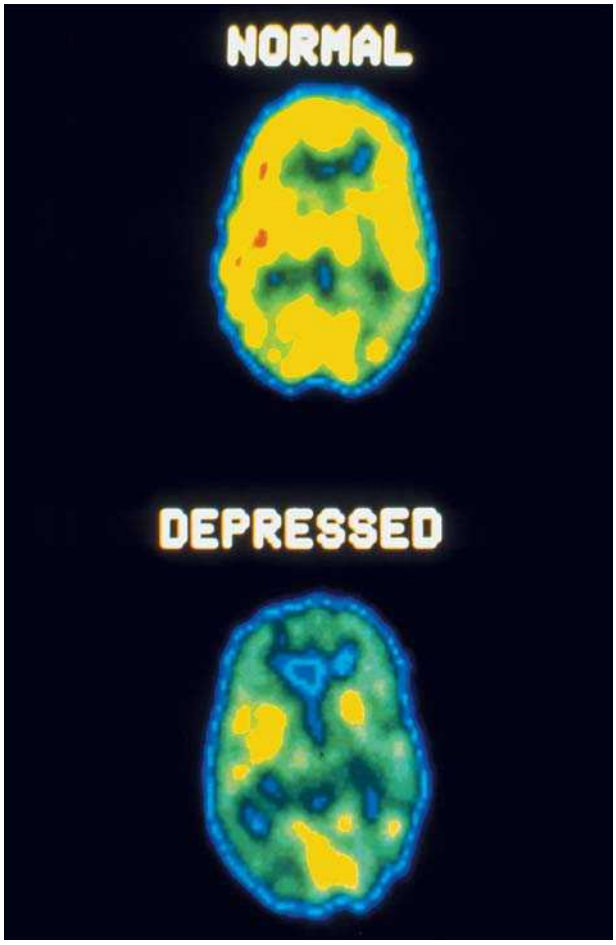
Interpersonal therapies—Also called "talking therapy," this type of psychological counseling is focused on determining how dysfunctional interpersonal relationships of the affected individual may be causing or influencing symptoms of depression.

Major depression—A psychological condition in which the patient experiences one or more disabling attacks of depression that last two or more weeks.

Polygenic—A trait, characteristic, condition, etc. that depends on the activity of more than one gene for its emergence or expression.

Psychodynamic therapies—A form of psychological counseling that seeks to determine and resolve the internal conflicts that may be causing an individual to be suffering from the symptoms of depression.

Psychotherapy—Psychological counseling that seeks to determine the underlying causes of a patient's depression. The form of this counseling may be cognitive/behavioral, interpersonal, or psychodynamic.



Clinical depression can be detected by a CAT scan. These two images demonstrate the difference between normal brain activity and depressed brain activity. *(Photo Researchers, Inc.)*

Symptoms that characterize a manic state are: increased energy accompanied by a decreased need for sleep, a loss of inhibitions accompanied by inappropriate social behavior, excessive enthusiasm and verve, increased talking, poor judgment, a feeling of invincibility, grandiose thinking and ideas, unusual irritability, and increased sexual desire.

Diagnosis

Depression is notoriously difficult to diagnose because its symptoms are not readily apparent to the medical professional unless the patient first recognizes and admits to them. Once the individual seeks help for his or her symptoms, the first step in the diagnosis of a depressive disorder is a complete physical examination to rule out any medical conditions, viral infections, or currently used medications that may produce the effects also seen in depression. Alcohol or other drug abuse as a possible cause of the observed symptoms should also be investigated. Once a physical basis for these symptoms is eliminated, a complete psychological exam should be undertaken. This examination consists of a mental status examination; a complete history of both current and previously experienced symptoms; and a family history.

The mental status examination is used to determine if a more severe psychotic condition is evident. This mental status examination will also determine whether the depressive disorder has caused changes in speech or thought patterns or memory that may indicate the presence of a depressive disorder. The complete psychological exam also includes a complete history of the symptoms being experienced by the affected individual. This history includes the onset of the symptoms, their duration, and whether or not the affected individual has had similar symptoms in the past. In the case of past symptoms, a treatment history should be completed to assess whether these symptoms previously responded to treatment, and if so, which treatments were effective. The final component of the complete psychological exam is the family history. In cases where the affected individual has had similarly affected family members a treatment history should also be completed, as much as possible, for these family members.

Treatment and management

Treatment of depression is on a case-by-case basis that is largely dependent on the outcome of the psychological examination. Some mildly affected individuals respond fully to psychotherapy and do not require medication. Some individuals affected with moderate or severe depression benefit from antidepressant medication. Most affected individuals respond best to a combination of antidepressant medication and psychotherapy: the medication to provide relatively rapid relief from the symptoms of depression and the psychotherapy to learn effective ways to manage and cope with problems and issues that may cause the continuation of symptoms or the onset of new symptoms of depression.

Various types of antidepressant medications are available for the treatment of depressive disorders. Many individuals affected with depression will go through a variety of antidepressants, or antidepressant combinations, before the best medication and dosage for them is identified. Almost all antidepressant medications must be taken regularly for at least two months before the full therapeutic effects are realized. A full course of medication is generally no shorter than 6 to 9 months to prevent recurrence of the symptoms. In individuals affected with bipolar disorder or chronic major depression, medication

may have to be continued throughout the remainder of their lives. These time-related conditions often pose problems in the management of individuals affected with depressive disorder. Many individuals with a depressive disorder discontinue their medications before the fully prescribed course for a variety of reasons. Some affected individuals feel side effects of the medications prior to feeling any benefits; others do not feel that the medication is helping because of the delay between the initiation of the treatment and the feelings of symptom relief; and many feel better prior to the full course and so cease taking the medication.

The three most commonly prescribed antidepressant drug classes consist of the older tricyclics (TCAs) and the two relatively new drug classes: the selective serotonin reuptake inhibitors (SSRIs) and the monoamine oxidase inhibitors (MAOIs). The most common TCAs are amitriptyline (Elavil), clomipramine (Anafranil), desipramine (Norpramin, Pertofrane), doxepin (Sinequan, Adapin), imipramine (Tofranil, Janimine), nortriptyline (Pamelor, Aventyl), protriptyline (Vivactil), and trimipramine (Surmontil). The most common SSRIs are: citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft). The most common MAOIs are: phenelzine (Nardil) and tranylcypromine (Parnate).

Many antidepressant medications cause side effects such as agitation, bladder problems, blurred vision, constipation, drowsiness, dry mouth, headache, insomnia, nausea, nervousness, or sexual problems. Most of these side effects wear off as the treatment course progresses. The tricyclics cause more severe side effects than the newer SSRIs or MAOIs.

St. John's wort is an herbal remedy that has been widely used to treat depressive disorders. In Germany, this herbal remedy is used more than any other antidepressant. As of early 2001, no scientific studies have been completed on the long-term effects of St John's wort in the treatment of depression. In 2000, the National Institutes of Health (NIH) completed patient enrollment in a three-year clinical study to study this herbal treatment of depression. The results of this study should be available in late 2003 or in 2004.

In the most severely affected individuals, or where antidepressant medications either have not worked or cannot be taken, electroconvulsive therapy (ECT) may be considered. In the ECT procedure, electrodes are put on specific locations on the head to deliver electrical stimulation to the brain. This electrical stimulation is designed to trigger a brief seizure within the brain. These seizures generally last approximately 30 seconds and are not consciously felt by the patient. ECT has been much improved in recent years; it is no longer the electro-shock treatment of nightmares, and its deleterious effects on long-term memory have been reduced. ECT treatments are generally administered several times a week as necessary to control the symptoms being experienced.

Several short-term (10 to 20 week) psychotherapies have also been demonstrated to be effective in the treatment of depressive disorders. These include interpersonal and cognitive/behavioral therapies. Interpersonal therapies focus on the interpersonal relationships of the affected individual that may both cause and heighten the depression. Cognitive/behavioral therapies focus on how the affected individual may be able to change his or her patterns of thinking or behaving that may lead to episodes of depression. Psychodynamic therapies, which generally are not short-term psychotherapies, seek to treat the individual affected with depressive disorder through a resolution of internal conflicts. Psychodynamic therapies are generally not initiated during major depression episodes or until the symptoms of depression are significantly improved by medication or one of the short-term psychotherapies.

Prognosis

Over 80% of individuals affected with a depressive disorder have demonstrated improvement after receiving the appropriate combination of treatments. A significant tragedy associated with depression is the failure of many affected individuals to realize that they have a treatable medical condition. Some affected individuals who do not receive treatment may recover completely on their own, but most will suffer needlessly. A small number of individuals with depressive disorder do not respond to treatment.

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ORGANIZATIONS

National Depressive and Manic Depressive Association. 730 N. Franklin, Suite 501, Chicago, IL 60610-7204. (800) 826-3632 or (312) 642-7243. <http://www.ndmda.org>.

National Foundation for Depressive Illness, Inc. PO Box 2257, New York, NY 10016. (212) 268-4260 or (800) 239-1265. <http://www.depression.org>.

National Institute of Mental Health. 6001 Executive Blvd., Rm. 8184, MSC 9663, Bethesda, MD 20892-9663. (301) 443-4513. Fax: (301) 443-4279. <http://www.nimh.nih.gov/publicat/index.cfm>.

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Paul A. Johnson

Diabetes

Definition

Diabetes mellitus describes a group of diseases in which there is an elevated level of the sugar glucose, the body's main source of energy for cellular functions, in the blood. The level of glucose, as well as other "fuel" molecules, is increased due to a disorder in the production or function of the hormone insulin. A range of health problems occurs primarily due to the damaging effects of elevated levels of glucose on blood vessels.

Description

To understand diabetes, it is important to understand how the hormone insulin functions in the breakdown and utilization of glucose. Insulin acts in two ways. It is necessary for the transport of glucose and other fuel molecules into the cells. It also regulates several pathways in metabolism that are important in the utilization of these fuel molecules. Insulin is made and released by specialized cells of the organ known as the pancreas. These *beta cells* of the pancreas release insulin when blood levels of glucose, amino acids, fatty acids, and ketones are high. These are all breakdown products of food, and an increase in their level in the blood signals that a person has recently eaten. The insulin acts to mobilize each of these fuel molecules so they can be used as energy to support cellular functions needed to maintain the body.

There are two main types of diabetes mellitus: type I and type II diabetes. While there are similarities, type I and type II diabetes differ in several aspects related to cause, symptoms, treatment, and associated risk factors. In addition, there are other less common forms of diabetes.

Type I diabetes

Also called insulin-dependent diabetes mellitus (IDDM), this is the most severe form of diabetes, in which shots of insulin are necessary on a daily basis. IDDM is thought to be an autoimmune condition in which one's own immune system attacks and destroys the insulin-producing cells of the pancreas. Insulin production is low or absent, and onset is generally in childhood or early adulthood. Affected individuals tend to be thin and prone to events in which ketones can become so high in the blood as to be potentially life-threatening, a complication called ketosis.

Type II diabetes

The most common type of diabetes, non-insulin dependent diabetes mellitus (NIDDM or type II), is the milder form of diabetes. Symptoms can generally be controlled with diet or oral medications that decrease blood sugar levels. True NIDDM does not develop into the insulin-dependent type of diabetes. In NIDDM, blood sugar levels become elevated because of resistance to the effects of insulin, which is usually present at normal levels. In other words, there may be plenty of insulin available, but the cells are not sensitive to insulin's effects. This results in the inability of insulin to move glucose to the inside of cells where it can be used. NIDDM typically develops after age 40, although it can occur at any age. Affected individuals tend to be obese and are not prone to ketosis.

Impaired glucose tolerance (IGT)

Impaired glucose tolerance is a symptom characterized by lab test results that indicate elevated blood glucose levels. The results are not abnormal enough to be called "diabetes." However, IGT may be an early sign of NIDDM, and is certainly a risk factor for developing NIDDM.

MODY

Maturity-onset diabetes of the young (MODY) is a rare form of NIDDM, in which onset is usually significantly earlier than in NIDDM. This form of diabetes shows a dominant **inheritance** pattern, unlike other forms of diabetes that are considered to be multifactorial (caused by a combination of multiple genetic and environmental factors). MODY is variable clinically within and between families.

Gestational diabetes

Also called diabetes of pregnancy, this form of the disease is often limited to the time during which a woman is pregnant. Management of glucose levels in affected women during pregnancy is very important, because high glucose levels can have serious, negative effects on the developing fetus. Gestational diabetes usually disappears after delivery. However, history of gestational diabetes increases a woman's risk of developing NIDDM in the future and of having gestational diabetes again in future pregnancies. Risk factors for gestational diabetes are similar to those for NIDDM.

Genetic profile

Like many common diseases, diabetes is caused by a combination of multiple environmental and genetic risk factors. The exact set of environmental and genetic factors that causes diabetes in any one individual is usually not known.

There are several known or suspected environmental factors that increase risk of developing diabetes and/or worsening complications. Environmental risk factors for developing IDDM are less well understood than for other types of diabetes. Infection by certain viruses has been implicated as a triggering event that can lead to the autoimmune reaction that causes disease in individuals with genetic susceptibility. Risk factors that are entirely or partially environmental have been implicated in NIDDM. These include obesity, low physical activity, poor dietary habits (high fat, salt, sugar intake), and alcohol and tobacco use. Cardiovascular risk factors—increased cholesterol and blood pressure, as well as others—also increase the chance for NIDDM to develop. Impaired glucose tolerance is a risk factor and can sometimes progress to NIDDM. For women, past history of gestational diabetes or delivery of a baby who was large-for-gestational-age also increases the chance of developing NIDDM. Ethnic background has a role in disease susceptibility for all types of diabetes, due to both genetic and environmental factors that may in part be affected by cultural practices.

Multiple genetic factors, both between individuals and often within a single affected individual, increase susceptibility to IDDM and NIDDM. Genetic factors are thought to be most important in individuals with a family history of the disease.

Heritability is the term that describes the genetic component causing a disease. It is a measure of the extent to which disease expression is the result of underlying genetic factors. One indication of the relative contribution of heritability in the causation of a particular disease is concordance.

Concordance describes the rate of similarity in disease expression between identical twins that share the same genetic material. As a general rule, the higher the concordance between identical twins, the greater the contribution of genetic factors to disease development. For example, the concordance for all types of diabetes ranges from 45-96%, indicating this percentage of diabetes can be attributed to genetic factors, with the remaining due to environmental factors. The specific genetic factors involved and their relative contributions toward diabetes development vary depending on the type of diabetes.

IDDM

Type I diabetes occurs when one's own immune system attacks and destroys the body's insulin-producing cells. There is a general population risk of 1/500 for developing IDDM. This risk increases when there is a family history or the presence of known genetic risk factors. The concordance for IDDM is generally thought to be less than 50%, suggesting that environmental factors must be present to trigger the development of the disease in individuals with genetic susceptibility. Even given this relatively low concordance, several genetic factors have been identified as established or suspected causes of IDDM susceptibility.

HLA ASSOCIATIONS HLA stands for *human leukocyte antigens* (also called **major histocompatibility complex**). HLA describes a group of proteins—genetically-determined and unique in each individual—that are important in helping the immune system distinguish 'self' from 'non-self' (foreign). Given their role in immunity, it seems intuitive that HLA types would be involved in susceptibility to this autoimmune form of diabetes. However, it is not yet clear if it is the HLA types themselves, or another closely linked **gene**, that increases risk.

There are several genes in the HLA gene family. Specific HLA-associations—consisting of variations of the HLA-DR gene—are thought to account for 60-70% of genetic susceptibility in IDDM. There is a significant understanding about the role of the HLA types, DR3 and DR4, in IDDM susceptibility.

HLA-DR alleles DR3 and DR4 are common in the general population. Almost half of all people in the United States have one or the other, which leads to a risk of 1/300 to 1/400 for developing IDDM. Two copies of DR3 or two copies of DR4—occuring in a very small percentage of the population—gives a risk of 1/150. Individuals having one copy each of DR3 and DR4 (1-3% of the population) is a combination that results in a 1/40 risk for developing IDDM. While less than 1% of individuals with these HLA types will develop diabetes, DR3 and/or DR4 are present in about 95% of all individuals with IDDM. While these HLA types confer suscep-

TABLE 1

Genes associated with NIDDM susceptibility

Gene (s)/Allele (s)	Study findings
HLA gene region on chromosome 6	Specific alleles confer susceptibility/protection in various ethnic groups.
Apolipoprotein genes	Inheritance of various forms (allele Lp (a) alleles of the apoA1/C3/B and apoE genes) may increase risk in certain ethnic groups. Individuals with Lp (a) have lower average insulin levels than individuals who did not inherit this form of the gene.
Lipoprotein lipase (LPL)	Changes in this gene (or genes nearby) may result in insulin resistance that can lead to NIDDM or 'Syndrome X' (a generic term for when an individual has obesity, high blood pressure, and NIDDM).
Fatty acid binding protein 2 on chromosome 4	May be associated with insulin resistance in Pima Indians and Mexican-Americans (no association in Caucasian families).
Glycogen synthase	A2 allele in Finns and A1 allele in French may increase risk of NIDDM and hypertension (no association in Caucasian families).
Beta3–adrenergic receptor	There is an association with insulin resistance, NIDDM, hypertension, and obesity in certain populations (Pima Indians, and to a lesser extent Mexican- and African-Americans) that have an increased frequency of a specific allele.
Gc gene	A variant form may have a role in insulin regulation in Dogrib Indians.

tibility to IDDM, other genetic or environmental factors must also be present in order for an individual to develop diabetes.

OTHER GENES ASSOCIATED WITH IDDM SUSCEPTIBILITY A genetic variation near the regulatory region of the insulin gene on chromosome 11 is widely accepted as a factor that confers IDDM susceptibility. This variation—called the 5' VNTR (variable number tandem repeat)—may contribute to susceptibility by influencing the regulation of the insulin gene, or by some other mechanism.

Several other genes or chromosomal locations have been identified and are being investigated as candidates that may contribute to genetic susceptibility for IDDM.

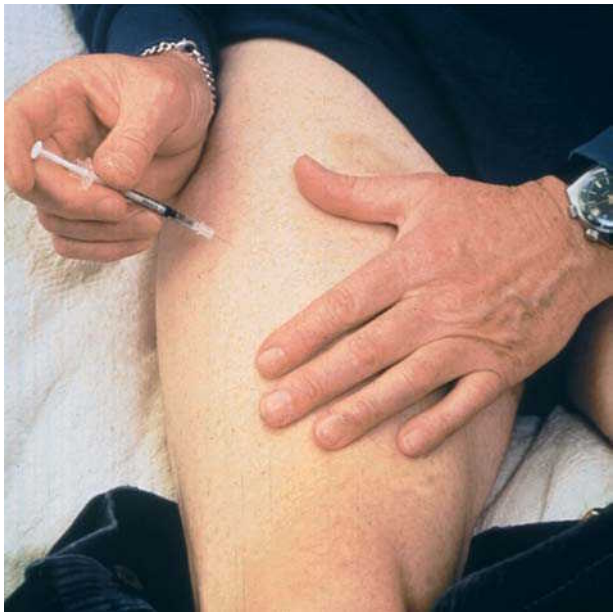
- Insulin receptor gene on chromosome 19
- Beta chain of the T-cell receptor on chromosome 7
- Immunoglobulin heavy chain (Gm) on chromosome 14
- Kidd blood group on chromosome 8
- IDDM3: chromosome 15 region
- IDDM4: chromosome 11 region near the fibroblast growth factor 3 gene
- IDDM5: chromosome 6 region
- IDDM7: chromosome 2 region near the HOXD8 gene
- IDDM8: chromosome 6 region
- Others: regions on **chromosomes** 3, 4, 13, and 18

It is thought that disease susceptibility is the result of these and other genetic factors acting independently and/or interacting with one another. There is still much to be learned about the identities, functions, and role in disease susceptibility for each of these implicated genes and chromosome regions.

SYNDROMES WITH IDDM AS A FEATURE In addition to susceptibility genes, there are several distinct syndromes that have IDDM as a potential feature. Additional characteristic features, aside from IDDM, mark these syndromes. The genetic basis for many of these conditions is known or suspected. These include syndromes with pancreatic disease (i.e. congenital absence of the pancreas and **cystic fibrosis**). There are multiple syndromes characterized by glucose intolerance due to or associated with a variety of other conditions including obesity, disease of the endocrine system, or diseases of metabolism. IDDM may also be seen in syndromes caused by mutations of the **DNA** of mitochondria—the cellular organelles that create energy. Mitochondrial DNA is only transmitted from the mother to each of her children, so such syndromes show a characteristic pattern of inheritance. IDDM (and NIDDM) tend to appear in conjunction with other features that are characteristic of these mitochondrial syndromes in affected families. MELAS syndrome—which is characterized by stroke-like episodes, muscle disease, and other symptoms—is one such example. It is caused by a mutation in the mitochondrial gene called tRNA Leu. Mutations in this gene can also result in a diabetes and deafness syndrome. A similar syndrome can also be caused by a large deletion of the mitochondrial DNA, called the 10.4kb deletion.

NIDDM

The genetic or heritability component of non-insulin dependent diabetes is thought to be greater than in IDDM. Studies estimate a concordance of up to 100%, with most studies estimating greater than 70%. Most experts interpret this relatively high concordance to reflect a somewhat high heritability. High concordance may also partly reflect the fact that the environment of all those studied—for example, in the United States—is



Diabetics must give themselves insulin shots to maintain proper blood sugar levels. *(Custom Medical Stock Photo, Inc.)*

highly uniform. Therefore, all those who have genetic susceptibility can be considered to be exposed to a sufficient number environmental risk factors to trigger NIDDM.

GENES ASSOCIATED WITH NIDDM SUSCEPTIBILITY

Genetic susceptibility in NIDDM is highly heterogeneous—meaning that variations in many different genes contribute to disease susceptibility. Although multiple susceptibility genes have been established or are suspected, major genes that confer a clearly high susceptibility do not play a major role—such as that seen with DR3 and DR4 in IDDM. NIDDM-associated genes include, but are not limited to, those found in the table.

MODY

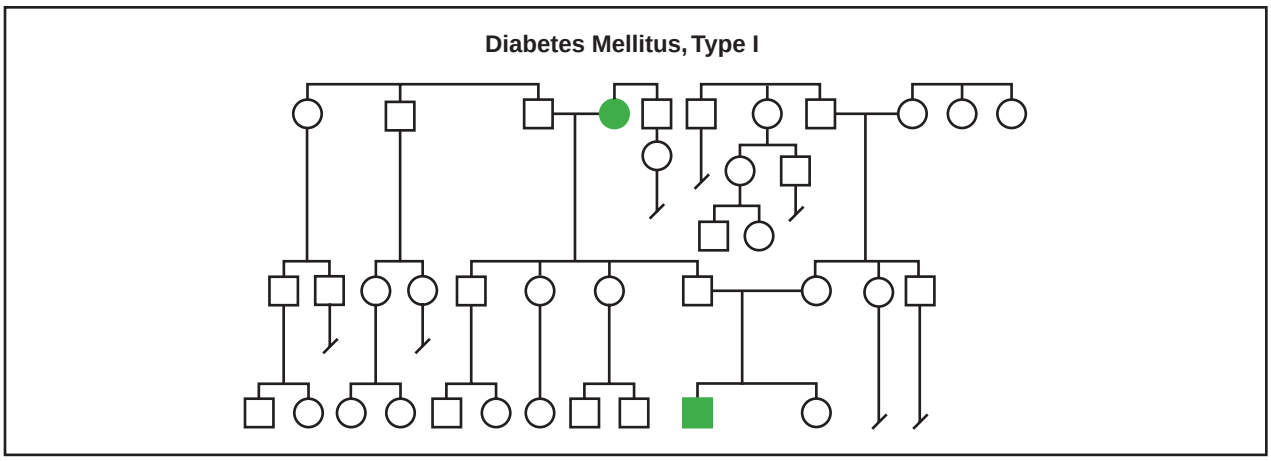
This dominantly inherited form of type II diabetes has been shown to be caused by alterations in at least four distinct genes. The majority of cases of MODY are due to mutations in the glucokinase gene (GCK) on chromosome 7. GCK plays a role in the regulation of glucose levels. Another gene, whose precise location and function is yet to be determined, is the next most common cause of MODY cases. The gene, called MODY3, is located on chromosome 12. A minority of MODY cases can be attributed to a presumed mutation in a gene on chromosome 20 (MODY1), whose exact location and function is not yet known. It is thought that there must be one or more additional genes yet to be identified that account for MODY in the remaining families with a dominant inheritance pattern. Parents, siblings, and children of affected individuals have a 50% chance of inheriting the same MODY-related mutation.

NIDDM due to insulin gene mutations

In some families, NIDDM appears to be inherited in an autosomal dominant fashion. Late onset of the disease may occur together with characteristic lab values. Some such families have been shown to carry specific mutations in the insulin gene. Three mutations are known and produce altered forms of the insulin protein that apparently do not function as well as the usual type of insulin. These include Insulin Los Angeles, Insulin Wakayama, and Insulin Chicago. Although only present in about 0.5% of people with NIDDM, these mutations can lead to a dominant form of the disease. Other alterations in the insulin gene—including other point mutations and a variation outside the gene called the 5' VNTR—may also contribute to NIDDM development or susceptibility in some populations.

Syndromes with NIDDM as a feature

As seen in IDDM, there are several distinct syndromes that have NIDDM as a potential feature. Aside from NIDDM, other characteristic features are present in each of these syndromes. The genetic basis for many of these conditions is known or suspected. These include syndromes with pancreatic disease (i.e. **hemochromatosis** and thalassemia) and syndromes due to mutations of the DNA of mitochondria—the cellular organelles that create energy. The latter includes MELAS syndrome, as well as a large deletion of mitochondrial DNA associated with diabetes and deafness. There are multiple syndromes with glucose intolerance resulting from or in association with a variety of other conditions. These include obesity, chromosomal imbalances, diseases of the endocrine system, or diseases of metabolism. As might be expected, mutations in the insulin receptor gene account for an increased risk for NIDDM. About 0.1% to 1% of the population carries such mutations, which leads to insulin resistance in some instances. Individuals who inherit two mutated copies of the insulin receptor gene may have extreme insulin resistance or diabetes. Some such individuals may have one of two rare syndromes. **Donohue syndrome** usually leads to death in the newborn period due to many serious complications resulting from very extreme insulin resistance. Rabson-Mendenhall syndrome is another very rare syndrome that affects multiple body systems and has been associated with the insulin receptor gene. Finally, mutations in this gene can lead to an inherited form of diabetes with acanthosis nigricans, a highly pigmented skin condition.



(Gale Group)

Demographics

Worldwide, diabetes mellitus represents a large proportion of the common, chronic diseases caused by multiple factors. Between 5% and 10% of adults in the Western world are affected by some form of diabetes. About 1/10,000 people have IDDM. The incidence of NIDDM is about three-fold that of IDDM—up to 5% of the U.S. population age 20-74. Up to an additional 11% have impaired glucose tolerance (IGT), which can represent an early stage of NIDDM.

Incidence rates of all types of diabetes vary among ethnic groups—a result of differing genetic and environmental backgrounds. For IDDM, incidence rates range from less than 1/100,000 among Japanese to greater than 25/100,000 among Scandinavians. Ethnic variation follows a different pattern for diabetes overall, which consists primarily of those with NIDDM and IGT. While NIDDM rates are very low among the Eskimo, IGT is very common.

Population studies suggest that there may be one or more major genes that influence diabetes susceptibility, particularly NIDDM susceptibility, in certain populations with high to very high incidence rates of clinical diabetes. These include Mexican Americans, Pima Indians, Oklahoma Seminoles, and several populations in the South Pacific including the Nauruans.

In other populations, increased incidences of NIDDM suggest the role of environmental factors in the disease's development. Changes in diet and lifestyle are implicated as contributing factors in the increased incidence seen by members of ethnic groups who have experienced Westernization due to immigration patterns or other cultural changes. Such factors may play a role in the increased incidence of NIDDM seen in African Americans, Japanese Americans, certain Native American groups, South Pacific Nauruans, and recently Westernized aboriginal Australians. Differences in incidence rates among various populations is a reflection of the multiple underlying genetic and environmental factors that contribute to the development of all types of diabetes mellitus.

Signs and symptoms

The onset of IDDM is marked by the sudden, dramatic appearance of one or more of the following symptoms:

- Frequent urination
- Extreme thirst and/or hunger
- Rapid weight loss
- Irritability
- Weakness and exhaustion
- Nausea and vomiting

NIDDM usually develops much more gradually. Symptoms can be subtle and include any of the above symptoms, in addition to the following:

- Itching
- Blurry vision
- Obesity
- Tingling or numbness in feet
- Slow healing of the skin or gums
- Recurrent bladder infections

Diabetes can affect many of the body's organs and systems. Individuals with IDDM are prone to a potentially life-threatening complication called ketosis, in which elevated tissue and fluid levels of ketones may lead to toxic results. People with diabetes are also prone

to infections. Infections of the kidney can lead to kidney disease and failure. A specific type of infection by an organism called *Mucormycosis* tends to occur following ketosis events in individuals with IDDM. This infection usually begins in the nasal passages and can become quite serious if it spreads to the soft tissues and bones of the face, the eye, the skull, or the brain. Gangrene can occur in individuals with poorly controlled disease and has the potential to result in limb amputation. There is an increased risk for cataracts, as well as **glaucoma**. Left untreated, such complications can lead to blindness. Vascular disease is common in both IDDM and NIDDM. Atherosclerosis—hardening of the arteries—can occur early and advance quickly, increasing the risk for stroke, kidney disease, and heart disease. Heart attack is the most common cause of death in diabetes. Disease of the peripheral blood vessels occurs commonly, particularly when kidney disease is also present. This can lead to increased bruising and development of ulcers, particularly in the leg.

MODY

Clinical severity is determined in part by the specific gene associated with disease within a family. MODY3 mutations result in the most severe clinical presentation, with 97% of cases having NIDDM, as opposed to impaired glucose tolerance. Individuals with MODY1 commonly experience vascular complications and require insulin in one-third of cases. Glucokinase (GCK) gene mutations, although the most common cause of MODY, tend to result in the mildest clinical picture. Approximately 46% have NIDDM, and the remaining individuals have IGT. Individuals with GCK-related MODY rarely need insulin and usually don't experience vascular complications.

Diagnosis

Diagnosis of diabetes can be based on the presence of suggestive symptoms, together with lab results that support the specific diagnosis.

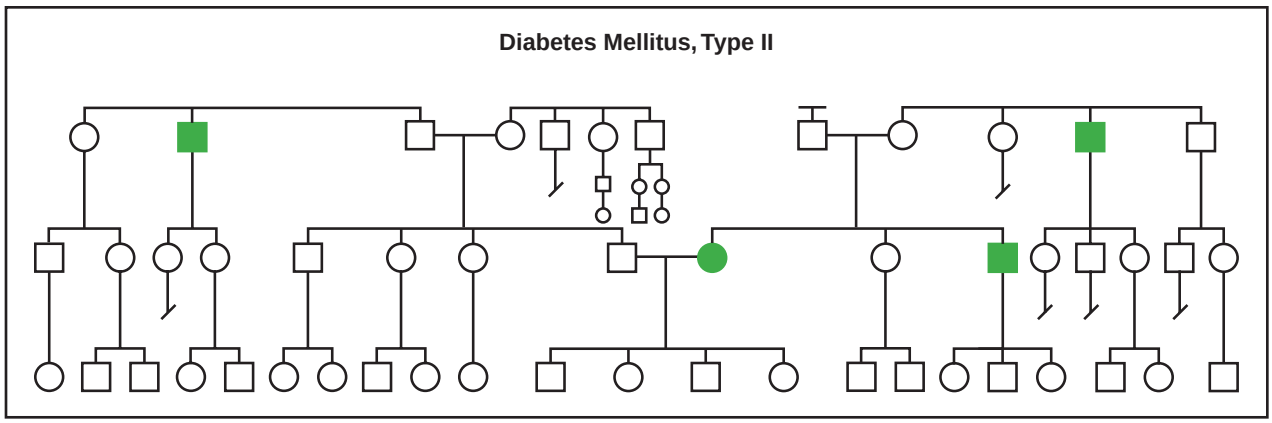
IDDM is a distinct disease that, in most all cases, is easy to diagnose based on clinical symptoms and lab values. The identification of certain autoantibodies (immune system proteins directed against 'self' tissues) is particularly helpful in diagnosing IDDM. The onset of IDDM is almost always rapid and dramatic. Rarely, onset can be gradual and result in a diagnostic dilemma in which it is difficult to distinguish from NIDDM, particularly in an individual who is age 35-50 and not obese. Testing for autoantibodies in such individuals can help distinguish the two diseases. Although not typically done, testing for the presence of HLA-DR3 and/or HLA-DR4 may also be informative. Individuals who have a relative with IDDM are also at increased risk of a variety of other autoimmune diseases—notably thyroid disease, autoimmune gastritis, and adrenal disease.

For individuals at increased risk of diabetes, a screening glucose tolerance test is recommended periodically and may identify diabetes before symptoms become obvious. Since gestational diabetes is such a common pregnancy complication, and the impact of unmanaged disease on the fetus is serious, all pregnant women are screened between the 24th and 28th weeks of pregnancy. For those at increased risk for NIDDM due to an affected relative, increased screening for risk factors for cardiovascular disease is also recommended.

Genetic testing

IDDM The fact that only about one-half of one percent of individuals with DR3 or DR4 develop IDDM is one indicator that HLA-typing on all individuals in the population is not a useful approach for determining IDDM risk. When there is a family history of IDDM, however, HLA-typing may have a role. When considering the risk for someone with a family history to develop IDDM, using the risk figures generated from large population studies based on family history alone (not HLA typing) is most appropriate. However, these risks could potentially be modified by HLA typing results. For example, there is a 1/14 risk for IDDM in the sibling of an affected individual. If HLA typing reveals that the sibling has inherited a completely different set of HLA types, the risk can be more accurately given as 1/100. On the other hand, if there are shared DR3/DR4 HLA types, this increases the risk to 1/5-1/4. Given HLA typing results or not, an individual with a sibling with IDDM is at sufficiently increased risk to warrant increased screening and education about early signs of the disease.

NIDDM NIDDM genetic susceptibility is highly heterogeneous. There are no single genes that alone increase susceptibility to a significantly high degree that testing should be considered. Like in IDDM, it is even more appropriate in NIDDM to discuss genetic susceptibility relative to population studies that determine risk based on family history alone (not based on **genetic testing**). These studies indicate that individuals with a parent, sibling, or child with NIDDM is at a 10-15% risk to develop NIDDM and a 20-30% risk for IGT, which may be an early sign of developing NIDDM. Symptoms that suggest a diagnosis of NIDDM can occur in younger individuals or those that do not fit the typical profile of someone with NIDDM in other ways (i.e. not obese). In these cases, genetic testing may play a role to help determine the true diagnosis of that individual and/or allow for a more accurate risk assessment.



(Gale Group)

MODY As discussed previously, there is a unique form of NIDDM called MODY. MODY is caused primarily by mutations in the glucokinase gene. Genetic testing for this form of diabetes is available and can be very helpful in diagnosis and risk assessment for other family members, if a glucokinase mutation is detected.

NIDDM DUE TO INSULIN GENE MUTATIONS In families with late onset of NIDDM, characteristic lab values, and a dominant pattern of inheritance, insulin gene testing is available. Other lab techniques are able to distinguish variant forms of insulin that result from known mutations. A positive genetic diagnosis of this type of NIDDM can be very helpful in risk assessment for other family members.

SYNDROMES WITH DIABETES AS A FEATURE There are also several underlying syndromes and diseases of which NIDDM, IDDM, and/or IGT are potential complications. These are generally accompanied by several other signs and symptoms. If one of these syndromes is suspected, the availability, benefits, and limitations of genetic testing can be considered. Mitochondrial DNA testing may be indicated in families that show NIDDM and/or IDDM transmitted only from mothers to children together with other features characteristic of mitochondrial syndromes. In some cases, genetic testing may be appropriate and can assist in diagnosis, medical management for other potential complications, and risk assessment for other family members.

Treatment and management

Management approaches for all types of diabetes are aimed at controlling blood glucose levels, preventing complications through lifestyle changes, and treating complications symptomatically as they arise.

The first step toward controlling blood glucose levels is monitoring the levels, which is done for all types of diabetes. This can be done daily with home glucose tests, as well as every few months through a physician using a test called the hemoglobin A1c test. When levels are abnormal, adjustments can be made in the timing and or quantity of dosages of insulin for IDDM and in oral glucose-lowering medications in NIDDM. Management of blood glucose levels is particularly important when diabetes occurs in pregnancy, to avoid the potential damaging effects on the developing fetus. Increased fetal monitoring and education is also a part of this management.

Lifestyle changes include changes in diet aimed at maintaining ideal body weight, lowering blood glucose levels, and preventing heart and blood vessel disease. Exercise also helps to maintain ideal body weight and helps the cardiovascular system remain healthy. In addition, exercise is important for helping insulin to function more efficiently in some forms of diabetes.

The acute and chronic complications of diabetes should be recognized and managed properly. Ketosis is an acute, potentially life-threatening complication that can be identified in its early stages by the presence of ketones in the urine. Home urine ketone tests are available and should be used—particularly in individuals with IDDM—when a person is sick or has a highly elevated blood glucose level prior to eating. Other medical complications—including infection, cataracts, and cardiovascular disease—are treated with conventional medicine as they arise.

Since diabetes can affect multiple body systems and has an impact on lifestyle on a daily basis, the disease is best managed by a multidisciplinary approach to care. Such an approach may involve many types of specialists, including physicians, dieticians, psychologists, high-risk obstetricians, genetic counselors, ophthalmologists, cardiologists, kidney specialists, and others.

Potential future treatments may include the long-range goal of **gene therapy**, particularly for IDDM. This therapy may be aimed at preventing or repairing damage to the insulin-producing pancreas, or restoring insulin production by some other means. There are several significant technical challenges that must be overcome, however, before gene therapy could become a reality.

Prognosis

As with many common chronic diseases, early diagnosis and treatment is very important to prevent diabetes-associated complications. Particularly for NIDDM, recognizing and modifying risk factors related to lifestyle plays a very important role and can often lead to the avoidance of complications or even the development of disease. With all types of diabetes, appropriate management can lead to increased quality of life and health.

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American Diabetes Association. 1701 N. Beauregard St., Alexandria, VA 22311. (703) 549-1500 or (800) 342-2383. <http://www.diabetes.org>.

Diabetes Action Research and Education Foundation. 426 C St. NE, Washington, DC 20002. <http://www.daref.org>.

Juvenile Diabetes Foundation International (JDF). 120 Wall St., New York, NY 10005. (212) 785-9500 x708 or (800) 533-2873. <http://www.jdf.org>.

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Jennifer Denise Bojanowski, MS, CGC

Diastrophic dysplasia

Definition

Diastrophic dysplasia (DTD) is a rare genetic disorder of bone growth and formation that is evident at birth.

Description

Diastrophic dysplasia is one of the genetic osteochondrodysplasias, a group of disorders characterized by abnormal growth and formation of bone and cartilage. The main features of DTD include: malformed ears, cleft palate, short limbs, short stature, spinal and joint deformities, and abnormalities of the bones of the hands and feet. Although children with DTD may experience delays in motor development (e.g. walking at a later age than expected), they are of normal intelligence. The syndrome derives its name from the Greek word, *diastrophos*, meaning twisted or crooked. Maroteaux and Lamy first used the term diastrophic dysplasia in 1960 to describe three of their patients and eleven other cases already reported in the literature. Since then, at least 300 cases of DTD have been described. Diastrophic dysplasia is also known as diastrophic nanism or diastrophic dwarfism and is abbreviated as DTD or DD.

Genetic profile

The **gene** responsible for DTD, known as the diastrophic dysplasia sulfate transporter gene (DTDST gene), is located at the end of the long arm of chromosome 5, at position 5q32-33. The DTDST gene produces a protein

that functions as a channel and transports sulfate across the cell membrane. DTD is inherited in an autosomal recessive manner. Affected individuals have a mutation in both copies of their DTDST gene; they inherit one mutation from each parent. Parents of affected individuals are carriers; they have a mutation in one copy of their DTDST gene and are without symptoms of the disorder.

Most bone in the body begins as cartilage and later hardens (ossifies) to form bone. In certain parts of the body such as the rib, auricle, and joints, cartilage does not ossify; it remains as cartilage and functions as load-bearing or shock-absorbing tissue. Cartilage contains sulfur-containing compounds, known as proteoglycans. It is thought that abnormal function of the DTD sulfate transporter leads to insufficient sulfate uptake by proteogycans in the cartilage. This undersulfation results in weakness and distortion of the cartilage. The exact mechanism by which this occurs is not fully understood.

Three other genetic skeletal dysplasias: recessively inherited multiple epiphyseal dysplasia (rMED), atelosteogenesis type 2 (AO-2), and **achondrogenesis** type IB (ACG-IB), are also due to mutations in the DTDST gene. When compared to DTD, both AO-2 and ACG-1B are more severe skeletal dysplasias, with the latter being a lethal disorder. Recessively inherited MED is a relatively mild condition. This broad range in severity, from mild to fatal, is attributed to the different types and combinations of genetic mutations within the DTDST gene that are responsible for these four related diseases.

Demographics

Diastrophic dysplasia is a rare disorder in most parts of the world except in Finland where the incidence of the disease is estimated at one in every 32,600 live births. Approximately 1–2% of Finnish people are DTD carriers. Most Finnish DTD gene carriers possess the same ancestral mutation, known as DTDST (Fin). The high frequency of this single mutation in Finland is attributed to a founder effect.

Signs and symptoms

Diastrophic dysplasia is a variable condition that tends to become more severe with age. Many manifestations of the disorder are prenatal in onset and are therefore apparent at birth.

Growth

Diastrophic dysplasia is considered a short-limbed skeletal dysplasia because the limbs are disproportionately short for the overall height of the individual. The newborn with DTD tends to be short with an average birth length of 16.5 in (42 cm). This growth failure continues throughout childhood and is progressive in nature. The degree of deformity caused by orthopedic complications of this disorder can influence overall height. A wide range of final adult heights has been reported with lower limits at 2 ft 10 in (86 cm) and 3 ft 5 in (104 cm) and upper limits at 4 ft 5 in (135.7 cm) and 4 ft 3 in (129 cm) for males and females respectively. On x ray, the limb bones appear short and thick with broad metaphyses and flattened, irregular epiphyses.

Craniofacial

One of the most distinct features of DTD is the so-called “cauliflower ear.” In over 80% of infants with DTD, fluid-filled cysts appear on the outer ear (pinnae) during the first few weeks of life. These cysts later calcify and may eventually ossify to form bone. In as many as 75% of individuals with DTD, some form of cleft palate is present. Although individuals with DTD may have a small chin (micrognathia), the head is otherwise normal in size.

Thoracic

Occasionally there may be abnormalities of cartilage in the trachea, larynx, and bronchi, which may lead to a life-threatening complication—collapse of the airways—especially in early infancy.

Spinal

Spina bifida occulta in the neck (cervical) and upper back (thoracic) region is the most common spinal abnormality found in DTD and is present in over 50% of cases. In spina bifida occulta there is incomplete closure of bones of the spinal column. Other common spinal abnormalities include progressive curvature of the spine, either from front to back (kyphosis) or from side to side (**scoliosis**). Kyphosis in the neck region (cervical kyphosis) is present in at least 30% of affected individuals and is usually evident at birth. This type of spine curvature usually resolves over time without treatment. In severe cases however, cervical kyphosis can lead to respiratory problems. Scoliosis, which is generally not present at birth, may appear at an early age and become problematic in early adolescence. Nearly 50% of females and at least 20% of males will develop scoliosis.

Joint

Joint changes in diastrophic dysplasia are progressive in nature and can be a painful complication of this disorder. Individuals with DTD may experience limited mobility and/or permanent immobility (contractures),

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Cartilage—Supportive connective tissue which cushions bone at the joints or which connects muscle to bone.

Chondrocyte—A specialized type of cell that secretes the material which surrounds the cells in cartilage.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Clubfoot—Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DNA mutation analysis—A direct approach to the detection of a specific genetic mutation or mutations using one or more laboratory techniques.

Dysplasia—The abnormal growth or development of a tissue or organ.

Epiphyses—The growth area at the end of a bone.

Fibroblast—Cells that form connective tissue fibers like skin.

Founder effect—increased frequency of a gene mutation in a population that was founded by a small ancestral group of people, at least one of whom was a carrier of the gene mutation.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Linkage analysis—A method of finding mutations based on their proximity to previously identified genetic landmarks.

Metacarpal—A hand bone extending from the wrist to a finger or thumb.

Metaphyses—The growth zone of the long bones located between the epiphyses the ends (epiphyses) and the shaft (diaphysis) of the bone.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nanism—Short stature.

Sulfate—A chemical compound containing sulfur and oxygen.

Vertebra—One of the 23 bones which comprise the spine. *Vertebrae* is the plural form.

especially in the knees and shoulders. The joints in an individual with DTD are also prone to partial or complete dislocations in the shoulders, hips, kneecaps, and elbows.

Hands and feet

The hands of a child with diastrophic dysplasia are distinct. The fingers are short (**brachydactyly**) and there may be fusion of the joints between the bones of the fingers (symphalangism). The metacarpal bone of the thumb is short and oval-shaped; these bony deformations cause the thumb to deviate away from the hand and assume the appearance of the so-called "hitchhiker thumb," a classic feature of DTD. The bony changes in the feet are similar to those found in the hands. The great toes may deviate outward, much like the thumbs. **Clubfoot** deformity (talipes), due to abnormal formation

and limited mobility of the bones of the feet, is a common birth defect found in newborns with DTD.

Diagnosis

At birth the diagnosis of diastrophic dysplasia is based on the presence of the characteristic physical and radiologic (x ray) findings. DNA mutation analysis may be helpful in confirmation of a suspected diagnosis. In those rarer cases where DNA mutation analysis does not detect changes, a laboratory test that measures the uptake of sulfate by fibroblasts or chondrocytes may be useful in making a diagnosis.

If there is a family history of diastrophic dysplasia and DNA is available from the affected individual, then prenatal diagnosis using DNA methods, either mutation analysis or linkage analysis, may be possible. DNA mutation analysis detects approximately 90% of DTDST mutations in suspected patients. In patients where the mutations are unknown or undetectable, another DNA method known as linkage analysis may be possible and, if so, it can usually distinguish an affected from an unaffected pregnancy with at least 95% certainty. In linkage analysis, DNA from multiple family members, including the person with DTD, is required. DNA-based testing can be performed through chorionic villus sampling or through **amniocentesis**.

If DNA-based testing is not possible, prenatal diagnosis of diastrophic dysplasia in an at-risk pregnancy may be made during the second and third trimesters through ultrasound. The ultrasound findings in an affected fetus may include: a small chin (micrognathia), abnormally short limbs, inward (ulnar) deviation of the hands, the "hitchhiker" thumb, clubfeet, joint contractures, and spinal curvature.

General population carrier screening is not available except in Finland where the frequency of a single ancestral mutation is high.

Treatment and management

There is currently no treatment that normalizes the skeletal growth and development in a child with diastrophic dysplasia. The medical management and treatment of individuals with DTD generally requires a multidisciplinary team of specialists that should include experts in orthopedics. At birth it is recommended that a neonatologist be present because of the potential for respiratory problems. Surgery may be indicated in infancy if congenital abnormalities such as open cleft palate and/or clubfoot deformity are present. Throughout childhood and adulthood, bracing, surgery, and physical therapy are measures often used to treat the spinal and joint deformities of DTD. Such measures, however, may not fully correct these deformities.

Due to the significant short-limbed short stature associated with diastrophic dysplasia, certain modifications to home, school, and work environments are necessary in order for a person with DTD to perform daily tasks. Occupational therapy may help affected individuals, especially children, learn how to use assistive devices and to adapt to various situations.

Prognosis

In infancy there is an increased mortality rate, as high as 25%, due to respiratory complications caused by weakness and collapse of the cartilage of the wind pipe (trachea) and/or the voice box (larynx), conditions which may require surgical intervention. Some forms of cleft palate and micrognathia may be life threatening in early life as they can result in respiratory obstruction. Severe spinal abnormalities such as cervical kyphosis may also cause respiratory problems. After the newborn period, the life span of an individual with DTD is usually normal with the exception of those cases where spinal cord compression occurs as a result of severe cervical kyphosis with vertebrae subluxation. Spinal cord compression is a significant medical problem that can lead to muscle weakness, paralysis, or death. In a susceptible individual, spinal cord compression may occur for the first time during surgery due to the hyperextended neck position used during intubation. Other anesthetic techniques may be indicated for such cases.

People with diastrophic dysplasia are of normal intelligence and are able to have children. Since many of the abnormalities associated with DTD are relatively resistant to surgery, many individuals with DTD will have some degree of physical handicap as they get older. They may continue to require medical management of their spinal and joint complications throughout adult life.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923 (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Diastrophic Help Web Site. <http://pixelscapes.com/ddhelp/>.

The Kathryn and Alan C. Greenberg Center for Skeletal Dysplasias Web Page. <http://www.med.jhu.edu/Greenberg.Center/Greenberg.htm>.

Dawn Cardeiro, MS, CGC

Diffuse angiokeratomia *see* **Fabry disease**

Disorder of cornification 10 *see* **Sjögren Larsson syndrome**

Distal arthrogryposis syndrome

Definition

Distal arthrogryposis syndrome is a rare genetic disorder in which affected individuals are born with a characteristic bending at the joints of the hands and feet. A contracture is the word used to describe what happens at the joints to cause this bending. In addition to contractures of the hand and feet, individuals with distal arthrogryposis are born with a tightly clenched fist and overlapping fingers.

Description

The word arthrogryposis means a flexed (bent) or curved joint. Distal means the furthest from any one point of reference or something that is remote. Therefore, distal arthrogryposis syndrome causes the joints at the most remote parts of our limbs, the hands and feet, to be flexed.

Consistent fetal movement during pregnancy is necessary for the development of the joints. Without regular motion, the joints become tight resulting in contractures. The first cases of arthryogryposis were identified in 1923. Arthryogryposis multiple congenital (AMC) is also referred to as fetal akinesia/hypokinesia sequence that is not a disorder, but describes what happens when there is no fetal movement during fetal development. The reasons for lack of fetal motion include neurologic, muscular, connective tissue, or skeletal abnormalities or intrauterine crowding. There are various disorders that involve some form of arthrogryposis.

Distal arthrogryposis was identified as a separate genetic disorder in 1982. Two types of distal arthrogryposis have been identified. Type 1 or typical distal arthrogryposis, is used to describe individuals with distal contractures of the hands and feet, characteristic positioning of the hands and feet, and normal intelligence. Type 2 distal arthrogryposis is known as the atypical form. It is characterized by additional birth defects and mild intellectual delays.

There are other syndomes which include arthrogryposis, however distal arthrogryposis has been characterized as its own syndrome by its **inheritance** pattern. In addition to the inheritance pattern, there are other features that differentiate this type of arthrogryposis from other forms. Some of these features include a characteristic position of the hands at birth; the fists are clenched and the fingers are bent and overlapping. In addition, problems with the positioning of the feet, called **clubfoot** is often seen in these individuals. Another distinguishing characteristic is an extremely wide variability in the severity and number of joint contractures someone may exhibit. This variability is often noticed between two affected individuals from the same family.

Genetic profile

Distal arthrogryposis syndrome is inherited in an autosomal dominant manner. Autosomal dominant inheritance patterns only require one genetic mutation on one of the chromosome pairs to exhibit symptoms of the disease. **Chromosomes** are the structures that carry genes. Genes are the blueprints for who we are and what we look like. Humans have 23 pairs, or 46 total chromosomes in every cell of their body. The first 22 chromosomes are numbered 1–22 and are called autosomes. The remaining pair is assigned a letter either an X or a Y and are the sex determining chromosomes. A typical male is described as 46, XY. A typical female is 46, XX.

Each parent contributes one of their paired chromosomes to their children. Before fertilization occurs, the father's sperm cell divides in half and the total number of chromosomes reduces from 46 to 23. The mother's egg cell undergoes the same type of reduction as well. At the

time of conception, each parent contributes 23 chromosomes, one of each pair, to their children. All of the genetic information is contained on each chromosome.

If either the father or the mother is affected with distal arthrogryposis, there is a 50% chance they will pass on the chromosome with the **gene** for this disease to each of their children. The specific gene for distal arthrogryposis is not known, however we do know that it is located on chromosome number 9.

The symptoms of distal arthrogryposis can be different between two affected relatives. For example, a mother may have contractures in all of her joints, but her child may only be affected with contractures in the hands. Because of this variability in the symptoms of this disease, it is believed there is more than one **gene mutation** that causes distal arthrogryposis. As of 2001, the only gene thought to cause this disease is on chromosome number 9. The exact location and type of genetic mutation on chromosome 9 is not known and therefore, the only **genetic testing** available as of 2001 is research based.

KEY TERMS

Amniotic fluid—The fluid which surrounds a developing baby during pregnancy.

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Flexion—The act of bending or condition of being bent.

Inheritance pattern—The way in which a genetic disease is passed on in a family.

Neurologic—Pertaining the nervous system.

Trisomy 18—A chromosomal alteration where a child is born with three copies of chromosome number 18 and as a result is affected with multiple birth defects and mental retardation.

Ultrasound evaluation—A procedure which examines the tissue and bone structures of an individual or a developing baby.

Demographics

Distal arthrogryposis can affect individuals from all types of populations and ethnic groups. This disease can affect both males and females. There have been only a handful of individuals described with this type of arthrogryposis. The physician, Dr. Hall, who named the disorder in 1982, had initially identified 37 patients with type 1 and type 2 distal arthrogryposis syndrome. She identified 14 individuals with type 1 and 23 individuals with type 2. Since then, numerous other individuals have been diagnosed with distal arthrogryposis. The exact incidence has not been reported in the literature.

Signs and symptoms

At birth, many individuals have been diagnosed based on their characteristic hand positioning. Virtually all individuals with distal arthrogryposis are born with their hands clenched tightly in a fist. The thumb is turned inwards lying over the palm, called abduction. The fingers are also overlapping on eachother. This hand positioning is also characteristic of a more serious condition called **trisomy 18**. The majority of patients with distal arthrogryposis will also have problems with the positioning of their feet. Many patients will have some form of clubfoot, where the foot is twisted out of shape or position. Another word for clubfoot is talipes.

In addition to the hand and foot involvement, a small percentage of patients will have a dislocation or separation of the hip joint as well as difficulty bending at the hips and tendency for there to be a slight degree of unnatural bending at the hip joints. The knees may also exhibit similar problems of being slightly bent and fixed at that point. Few individuals are born with stiff shoulders.

Type 2 distal arthrogryposis syndrome includes other birth defects not seen in type 1 individuals. For example, type 2 distal arthrogryposis involves problems with the closure of the lip called cleft lip or an opening in the roof of the mouth called cleft palate.

Other abnormalities seen in type 2 distal arthrogryposis include a small tongue, short stature, a curvature of the spine, more serious joint contractures, and mental delays.

Diagnosis

The diagnosis of distal arthrogryposis can sometimes be made during pregnancy from an ultrasound evaluation. An ultrasound may detect the characteristic hand finding as well as the flexion deformities of both the hands and the feet. An affected fetus may have difficulty swallowing and this is exhibited on an ultrasound evaluation as extra amniotic fluid surrounding the baby called polyhydramnios. Another very important and specific diagnositic sign for distal arthrogryposis during a pregnancy is no fetal movement. Ultrasound findings have been detected as early as 17 weeks of a pregnancy.

After birth, a diagnosis is made by a physician performing a physical examination of a baby suspected of having this disorder. If a baby is affected with type 2 distal arthrogryposis, they may have a difficult time eating properly. As of 2001, the only type of genetic testing available is research based. Because there is likely more than one gene that causes the disease, the genetic testing being performed at this time is not yet offered to affected individuals in order to confirm a diagnosis.

Treatment and management

The treatment for individuals with distal arthrogryposis is adjusted to the needs of the affected child. With therapy after birth to help loosen the joints and retrain the muscles, most individuals do remarkably well. The hands do not remain clenched an entire lifetime, but will eventually unclench. Sometimes the fingers will remain bent to some degree. Clubfoot can usually be corrected so that the feet can be positioned to be straight.

Prognosis

The prognosis depends on how severely affected an individual is and how many joints are involved. Some of the more severe cases may be associated with an early death due to sudden respiratory failure and difficulty breathing properly. The majority of individuals with distal arthrogryposis do very well after receiving the necessary therapies and sometimes surgery to correct severe joint contractions.

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Katherine S. Hunt, MS

DNA (deoxyribonucleic acid)

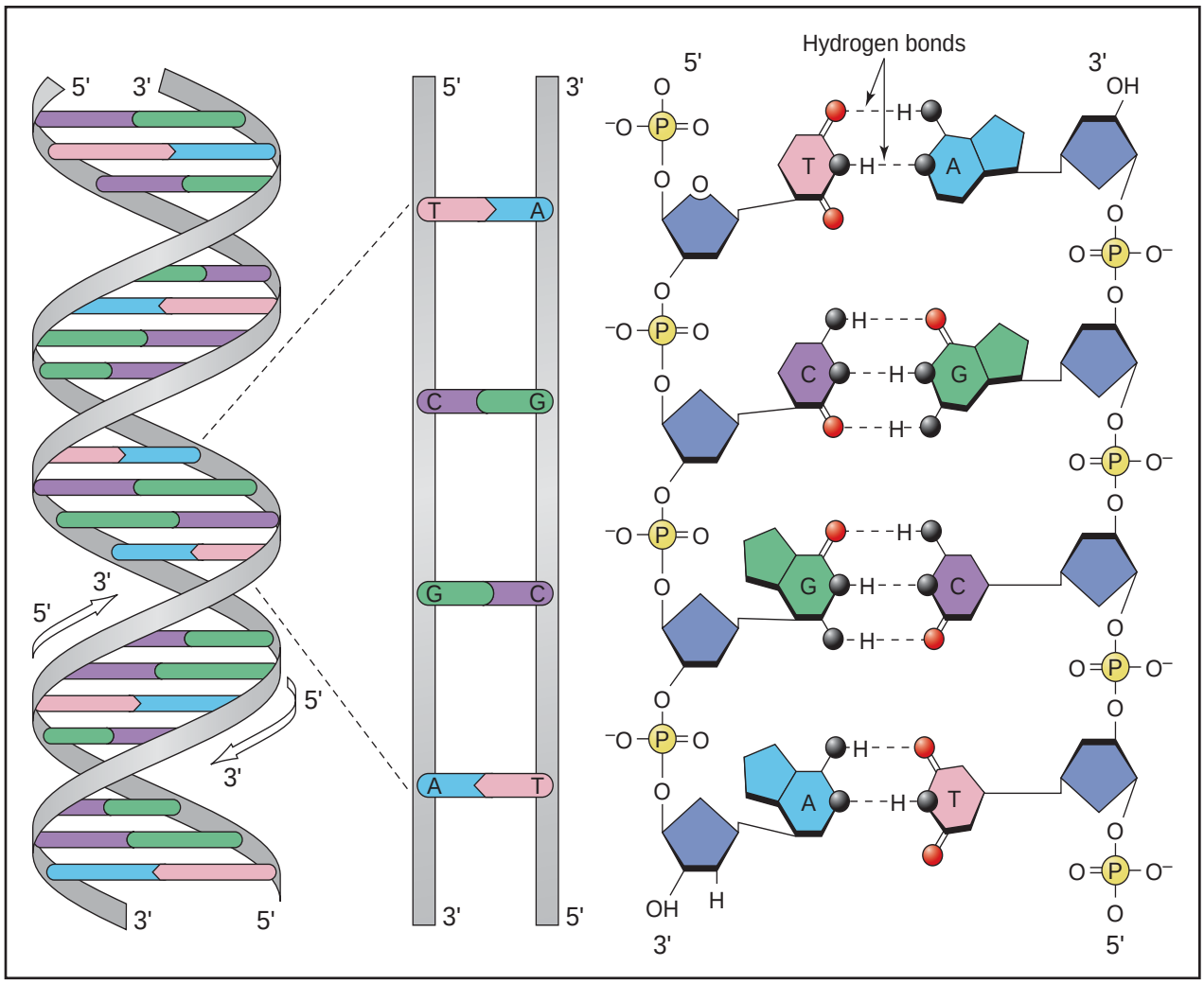
Genetics is the science of heredity that involves the study of the structure and function of genes and the methods by which genetic infomation contained in genes is passed from one generation to the next. The modern science of genetics can be traced to the research of Gregor Mendel (1823–1884), who was able to develop a series of laws that described mathematically the way hereditary characteristics pass from parents to offspring. These laws assume that hereditary characteristics are contained in discrete units of genetic material now known as genes.

The story of genetics during the twentieth century is, in one sense, an effort to discover the **gene** itself. An important breakthrough came in the early 1900s with the work of the American geneticist, Thomas Hunt Morgan (1866–1945). Working with fruit flies, Morgan was able to show that genes are somehow associated with the **chromosomes** that occur in the nuclei of cells. By 1912, Hunt's colleague, American geneticist A. H. Sturtevant (1891–1970) was able to construct the first chromosome map showing the relative positions of different genes on a chromosome. The gene then had a concrete, physical referent; it was a portion of a chromosome.

During the 1920s and 1930s, a small group of scientists looked for a more specific description of the gene by focusing their research on the gene's molecular composition. Most researchers of the day assumed that genes were some kind of protein molecule. Protein molecules are large and complex. They can occur in an almost infinite variety of structures. This quality is expected for a class of molecules that must be able to carry the enormous variety of genetic traits.

A smaller group of researchers looked to a second family of compounds as potential candidates for the molecules of heredity. These were the nucleic acids. The nucleic acids were first discovered in 1869 by the Swiss physician Johann Miescher (1844–1895). Miescher originally called these compounds "nuclein" because they were first obtained from the nuclei of cells. One of Miescher's students, Richard Altmann, later suggested a new name for the compounds, a name that better reflected their chemical nature: nucleic acids.

Nucleic acids seemed unlikely candidates as molecules of heredity in the 1930s. What was then known about their structure suggested that they were too simple to carry the vast array of complex information needed in a molecule of heredity. Each nucleic acid molecule consists of a long chain of alternating sugar and phosphate fragments to which are attached some sequence of four of five different nitrogen bases: adenine, cytosine, guanine, uracil and thymine (the exact bases found in a molecule depend slightly on the type of nucleic acid).



The structure of a DNA molecule. *(Gale Group)*

It was not clear how this relatively simple structure could assume enough different conformations to "code" for hundreds of thousands of genetic traits. In comparison, a single protein molecule contains various arrangements of twenty fundamental units (amino acids) making it a much better candidate as a carrier of genetic information.

Yet, experimental evidence began to point to a possible role for nucleic acids in the transmission of hereditary characteristics. That evidence implicated a specific sub-family of the nucleic acids known as the deoxyribonucleic acids, or DNA. DNA is characterized by the presence of the sugar deoxyribose in the sugar-phosphate backbone of the molecule and by the presence of adenine, cytosine, guanine, and thymine, but not uracil.

As far back as the 1890s, the German geneticist Albrecht Kossel (1853–1927) obtained results that pointed to the role of DNA in heredity. In fact, historian John Gribbin has suggested that the evidence was so clear that it "ought to have been enough alone to show that the hereditary information... *must* be carried by the DNA." Yet, somehow, Kossel himself did not see this point, nor did most of his colleagues for half a century.

As more and more experiments showed the connection between DNA and genetics, a small group of researchers in the 1940s and 1950s began to ask how a DNA molecule could code for genetic information. The two who finally resolved this question were a somewhat unusual pair, James Watson, a 24-year old American trained in genetics, and Francis Crick, a 36-year old Englishman, trained in physics and self-taught in chemistry. The two met at the Cavendish Laboratories of Cambridge University in 1951, and became instant friends. They were united by a common passionate belief that the structure of DNA held the key to understanding how genetic information is stored in a cell and how it is transmitted from one cell to its daughter cells.

In one sense, the challenge facing Watson and Crick was a relatively simple one. A great deal was already known about the DNA molecule. Few new discoveries were needed, but those few discoveries were crucial to solving the DNA-heredity puzzle. Primarily the question was one of molecular architecture. How were the various parts of a DNA molecule oriented in space such that the molecule could hold genetic information?

The key to answering that question lay in a technique known as x-ray crystallography. When x rays are directed at a crystal of some material, such as DNA, they are reflected and refracted by atoms that make up the crystal. The refraction pattern thus produced consists of a collection of spots and arcs. A skilled observer can determine from the refraction pattern the arrangement of atoms in the crystal.

The technique is actually more complex than described here. For one thing, obtaining satisfactory x-ray patterns from crystals is often difficult. Also, interpreting x-ray patterns—especially for complex molecules like DNA—can be extremely difficult.

Watson and Crick were fortunate in having access to some of the best x-ray diffraction patterns that then existed. These "photographs" were the result of work being done by Maurice Wilkins and Rosalind Elsie Franklin at King' s College in London. Although Wilkins and Franklin were also working on the structure of DNA, they did not recognize the information their photographs contained. Indeed, it was only when Watson accidentally saw one of Franklin's photographs that he suddenly saw the solution to the DNA puzzle.

Racing back to Cambridge after seeing this photograph, Watson convinced Crick to make an all-out attack on the DNA problem. They worked continuously for almost a week. Their approach was to construct tinkertoy-like models of the DNA molecule, shifting atoms around into various positions. They were looking for an arrangement that would give the kind of x-ray photograph that Watson had seen in Franklin's laboratory.

Finally, on March 7, 1953, the two scientists found the answer. They built a model consisting of two helices (corkscrew-like spirals), wrapped around each other. Each helix consisted of a backbone of alternating sugar and phosphate groups. To each sugar was attached one of the four nitrogen bases, adenine, cytosine, guanine, or thymine. The sugar-phosphate backbone formed the outside of the DNA molecule, with the nitrogen bases tucked inside. Each nitrogen base on one strand of the molecule faced another nitrogen base on the opposite strand of the molecule. The base pairs were not arranged at random, however, but in such a way that each adenine was paired with a thymine, and each cytosine with a guanine.

The Watson-Crick model was a remarkable achievement, for which the two scientists won the 1954 Nobel Prize in Chemistry. The molecule had exactly the shape and dimensions needed to produce an x-ray photograph like that of Franklin's. Furthermore, Watson and Crick immediately saw how the molecule could "carry" genetic information. The sequence of nitrogen bases along the molecule, they said, could act as a genetic code. A sequence, such as A-T-T-C-G-C-T . . . etc., might tell a cell to make one kind of protein (such as that for red hair), while another sequence, such as G-C-T-C-T-C-G . . . etc., might code for a different kind of protein (such as that for blonde hair). Watson and Crick themselves contributed to the deciphering of this genetic code, although that process was long and difficult and involved the efforts of dozens of researchers over the next decade.

Watson and Crick had also considered, even before their March 7th discovery, what the role of DNA might be in the manufacture of proteins in a cell. The sequence that they outlined was that DNA in the nucleus of a cell might act as a template for the formation of a second type of nucleic acid, **RNA** (ribonucleic acid). RNA would then leave the nucleus, emigrate to the cytoplasm and then itself act as a template for the production of protein. That theory, now known as the Central Dogma, has since been largely confirmed and has become a critical guiding principal of much research in molecular biology.

Scientists continue to advance their understanding of DNA. Even before the Watson-Crick discovery, they knew that DNA molecules could exist in two configurations, known as the "A" form and the "B" form. After the Watson-Crick discovery, two other forms, known as the "C" and "D" configurations, were also discovered. All four of these forms of DNA are right-handed double helices that differ from each other in relatively modest ways.

In 1979, however, a fifth form of DNA known as the "Z" form was discovered by Alexander Rich and his colleagues at the Massachusetts Institute of Technology. The "Z" form was given its name partly because of its zig-zag shape and partly because it is different from the more common A and B forms. Although Z-DNA was first recognized in synthetic DNA prepared in the laboratory, it has since been found in natural cells whose environment is unusual in some respect or another. The presence of certain types of proteins in the nucleus, for example, can cause DNA to shift from the B to the Z conformation. The significance and role of this most recently discovered form of DNA remains a subject of research among molecular biologists.

Judyth Sassoon, ARCS, PhD

Donohue syndrome

Definition

Donohue syndrome, also formerly called leprechaunism, is a genetic disorder caused by mutations in the insulin receptor **gene**. W. L. Donohue first described this rare syndrome in 1948.

Description

Donohue syndrome is a disorder that causes low birth weight, unusual facial features, and failure to thrive in infants. Donohue syndrome is associated with the over-development of the pancreas, a gland located near the stomach. It is also considered to be the most insulin resistant form of diabetes.

Donohue syndrome results from a mutation of the insulin receptor gene which prevents insulin in the blood from being processed. Therefore, even before birth, the fetus exhibits "insulin resistance" and has high levels of unprocessed insulin in the blood. Insulin is one of two hormones secreted by the pancreas to control blood sugar (glucose) levels. Donohue syndrome is known as a progressive endocrine disorder because it relates to the growth and functions of the endocrine system, the collection of glands and organs that deliver hormones via the bloodstream.

Hormones are chemicals released by the body to control cellular function (metabolism) and maintain equilibrium (homeostasis). These hormones are released either by the endocrine system or by the exocrine system. The endocrine system consists of ductless glands that secrete hormones into the bloodstream. These hormones then travel through the blood to the parts of the body where they are required. The exocrine system consists of ducted glands that release their hormones via ducts directly to the site where they are needed. The pancreas is both an endocrine and an exocrine gland. As part of the endocrine system, the pancreas acts as the original producer of estrogen and other sex hormones in fetuses of both sexes. It also regulates blood sugar through its production of the hormones insulin and glucagon. The pancreas releases insulin in response to high levels of glucose in the blood. Glucagon is released when glucose levels in the blood are low. These two hormones act in direct opposition to each other (antagonistically) to maintain proper blood sugar levels. As an exocrine gland, the pancreas secretes digestive enzymes directly into the small intestine.

In an attempt to compensate for the high blood insulin level, the pancreas overproduces glucagon as well as the female hormone estrogen and other related (estrogenic) hormones. As excess estrogen and related hormones are produced, they affect the development of the external and internal sex organs (genitalia) of the growing baby.

Insulin mediates the baby's growth in the womb through the addition of muscle and fat. A genetic link between fetal insulin resistance and low birthweight has been suggested. Without the proper processing of insulin, the fetus will not gain weight as fast as expected. Therefore, the effects of Donohue syndrome tend to become visible during the seventh month of development when the fetus either stops growing entirely or shows a noticeable slowdown in size and weight gain. This lack of growth is further evident at birth in affected infants, who demonstrate extreme thinness (emaciation), difficulty gaining weight, a failure to thrive, and delayed maturation of the skeletal structure.

Genetic profile

Donohue syndrome is a non-sex-linked (autosomal) recessive disorder. In 1988, Donohue syndrome was identified as the first insulin receptor **gene mutation** directly related to a human disease. The gene responsible for the appearance of Donohue syndrome is the insulin receptor gene located at 19p13.2. Over 40 distinct mutations of this gene have been identified. Besides Donohue syndrome, other types of non-insulin-dependent (Type II) **diabetes mellitus** (NIDDM) can result from mutations of this gene, including Rabson-Mendenhall syndrome and type A insulin resistance.

Demographics

Donohue syndrome occurs in approximately one out of every four million live births. As in all recessive **genetic disorders**, both parents must carry the gene mutation in order for their child to have the disorder. Therefore, Donohue syndrome has been observed in cases where the parents are related by blood (consanguineous). Parents with one child affected by Donohue syndrome have a 25% likelihood that their next child will also be affected with the disease.

Signs and symptoms

Infants born with Donohue syndrome have characteristic facial features that have been said to exhibit "elfin" or leprechaun-like qualities, such as: a smallish head with large, poorly developed and low-set ears; a flat nasal ridge with flared nostrils, thick lips, a greatly exaggerated mouth width, and widely spaced eyes. They will be very thin and have low blood sugar (hypoglycemia) due to their inability to gain nutrition through insulin pro-

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Consanguineous—Sharing a common bloodline or ancestor.

Endocrine system—A system of ductless glands that regulate and secrete hormones directly into the bloodstream.

Fibroblast—Cells that form connective tissue fibers like skin.

Hirsutism—The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

Histologic—Pertaining to histology, the study of cells and tissues at the microscopic level.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Insulin receptor gene—The gene responsible for the production of insulin receptor sites on cell surfaces. Without properly functioning insulin receptor sites, cells cannot attach insulin from the blood for cellular use.

Insulin resistance—An inability to respond normally to insulin in the bloodstream.

Insulin-like growth factor I—A hormone released by the liver in response to high levels of growth hormone in the blood. This growth factor is very similar to insulin in chemical composition; and, like insulin, it is able to cause cell growth by causing cells to undergo mitosis (cell division).

Pachyderma—An abnormal skin condition in which excess skin is produced that appears similar to that of an elephant (pachyderm).

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Serological—Pertaining to serology, the science of testing blood to detect the absence or presence of antibodies (an immune response) to a particular antigen (foreign substance).

cessing. They will exhibit delayed bone growth and maturation, and difficulty in gaining weight and developing (failure to thrive).

Donohue syndrome patients are prone to persistent and recurrent infections. Delayed bone growth not only leads to skeletal abnormalities, it also leads to a compromised immune system. Many of the chemicals used by the body to fight infection are produced in the marrow of the bones. When bone maturation is delayed, these chemicals are not produced in sufficient quantities to fight off or prevent infection.

At birth, affected individuals can also have an enlarged chest, with possible breast development, excessive hairiness (hirsutism), as well as overdeveloped external sex organs, because of increased estrogen production caused by an overactive pancreas. As an additional side effect of the increased sex hormones released in Donohue syndrome, these individuals often have extremely large hands and feet relative to their non-affected peer group. As the result of a lack of insulin, the infant is likely to have a relatively small amount of muscle mass, very little fat, and a distended abdomen (due to malnutrition). Additional symptoms of Donohue syndrome include pachyderma, or elephant skin, in which there is excess skin production causing large, loose folds; and abnormal coloration (pigmentation) of the skin. These individuals are also quite susceptible to both umbilical and inguinal hernias.

In addition to the defect in the insulin receptor gene, Donohue syndrome is associated with problems in the epidermal growth factor receptor, which controls growth of the skin. An abnormal functioning of the epidermal growth factor receptor has been identified in three unrelated individuals affected with Donohue syndrome. This suggests that the probable cause of leprechaunism is more than just the insulin receptor. These observations may help explain the physical symptom of pachyderma in those affected with Donohue syndrome. It has also been suggested that the high concentrations of insulin close to the cell membranes lead to receptor activity at these loca-

tions. This lowered growth hormone activity, in turn, causes slowed cellular growth which leads to systemic growth failure in affected patients.

Diagnosis

In families with a history of the disease, diagnosis *in utero* before birth of the fetus is possible through molecular **DNA** analysis of tissue samples from the chorionic villi, which are cells found in the placenta. After birth, the diagnosis of Donohue syndrome is usually made based on the blood tests that show severe insulin resistance coupled with hypoglycemia. The presence of several of the physical symptoms listed above in addition to positive results in a test for severe insulin resistance, such as an insulin receptor defect test or a fasting hypoglycemia test, is usually sufficient for a diagnosis of Donohue syndrome. The diagnosis of Donohue syndrome may be confirmed by observed cellular (histologic) changes in the ovaries, pancreas, and breast that are not normal for the age of the patient.

Treatment and management

Genetic counseling of parents with a Donohue syndrome affected child may help prevent the conception of additional children affected with this genetic disorder. After birth, affected infants may require treatment for malnutrition as well as insulin resistant diabetes. Patients with a demonstrated residual insulin receptor function may survive past infancy. In these cases, the treatment regimen must certainly include on-going insulin resistant diabetes care and dietetic counseling to assist with weight gain. It may also be necessary to administer growth hormone therapy to certain patients to spur growth, but this is only indicated in those individuals who show signs of functioning growth hormone receptors and no signs of higher than normal resistance to growth hormone.

The revolutionary impact of recombinant DNA technology, whereby scientists can mass produce genetic material for use in medicine, has made possible another treatment method which involves the introduction of recombinant human insulin-like growth factor 1 (rhIGF-1) into the body. A case study has been reported of a female affected with Donohue syndrome and low levels of insulin-like growth factor 1 (IGF-1), which is indicative of a higher than normal resistance to growth hormone.

Examination of the patient's fibroblasts showed normal binding of IGF-1 and normal functioning of these fibroblasts in response to IGF-1. Fibroblasts are connective tissue cells that accomplish growth in humans by differentiating into chondroblasts, collagenoblasts, and osteoblasts, all of which are the precursor cells necessary to produce bone growth in humans. This case report indicates that if enough IGF-1 could get to the fibroblasts in the patient's body, there is every reason to believe that these fibroblasts would function normally and mature into the precursor cells needed for bone growth. This finding made the patient an ideal candidate for rhIGF-1 treatments.

The long- and short-term effects on growth patterns and glucose metabolism in the patient were studied after the treatment with recombinant human insulin-like growth factor 1 (rhIGF-1). The rhIGF-1 that was not immediately utilized by the patient was rapidly destroyed in the cellular conditions produced by Donohue syndrome. Therefore, to maintain the desired levels of rhIGF-1 in the blood, the patient received rhIGF-1 both in injection form prior to every meal and via a continuous subcutaneous infusion method similar to that used to continuously pump insulin for some patients with diabetes. Recombinant human IGF-1 was administered to this patient over a period of six years with an observation of normal blood glucose levels and a return to normal growth patterns. Moreover, the treatment did not cause negative side effects. The results of this case study offer a promising new treatment for certain individuals affected with Donohue syndrome. As of 2001, other clinical studies of treatments with rhIGF-1 are in progress.

Prognosis

Individuals born with Donohue syndrome generally die in infancy from either malnutrition or recurrent and persistent infection. All individuals affected with Donohue syndrome that survive past infancy have severe mental retardation and profound motor skill impairment. Survival into childhood is thought to be due to some remaining insulin receptor function and the ability of extremely high insulin concentrations to transmit signals through alternate pathways.

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Children Living with Inherited Metabolic Diseases. The Quadrangle, Crewe Hall, Weston Rd., Crewe, Cheshire, CW1-6UR. UK 127 025 0221. Fax: 0870-7700-327. <http://www.climb.org.uk>.

National Center for Biotechnology Information. National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894. (301) 496-2475. <http://www.ncbi.nlm.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paul A. Johnson

Down syndrome

Definition

Down syndrome is the most common chromosome disorder and genetic cause of mental retardation. It occurs because of the presence of an extra copy of chromosome 21. For this reason, it is also called trisomy 21.

Description

When a baby is conceived, the sperm cell from the father and the egg cell from the mother undergo a reduction of the total number of **chromosomes** from 46 to 23. Occasionally an error occurs in this reduction process and instead of passing on 23 chromosomes to the baby, a parent will pass on 24 chromosomes. This event is called nondisjunction and it occurs in 95% of Down syndrome cases. The baby therefore receives an extra chromosome at conception. In Down syndrome, that extra chromosome is chromosome 21. Because of this extra chromosome 21, individuals affected with Down syndrome have 47 instead of 46 chromosomes.

Genetic profile

In approximately one to two percent of Down syndrome cases, the original egg and sperm cells contain the correct number of chromosomes, 23 each. The problem occurs sometime shortly after fertilization—during the phase when cells are dividing rapidly. One cell divides abnormally, creating a line of cells with an extra copy of chromosome 21. This form of genetic disorder is called mosaicism. The individual with this type of Down syndrome has two types of cells: those with 46 chromosomes (the normal number), and those with 47 chromosomes (as occurs in Down syndrome). Individuals affected with this mosaic form of Down syndrome generally have less severe signs and symptoms of the disorder.

Another relatively rare genetic accident that causes Down syndrome is called translocation. During cell division, chromosome 21 somehow breaks. The broken off piece of this chromosome then becomes attached to another chromosome. Each cell still has 46 chromosomes, but the extra piece of chromosome 21 results in the signs and symptoms of Down syndrome. Translocations occur in about 3–4% of cases of Down syndrome.

Once a couple has had one baby with Down syndrome, they are often concerned about the likelihood of future offspring also being born with the disorder. Mothers under the age of 35 with one Down syndrome-affected child have a 1% chance that a second child will also be born with Down syndrome. In mothers 35 and older, the chance of a second child being affected with Down syndrome is approximately the same as for any woman at a similar age. However, when the baby with Down syndrome has the type that results from a translocation, it is possible that one of the two parents is a carrier of a balanced translocation. A carrier has rearranged chromosomal information and can pass it on, but he or she does not have an extra chromosome and therefore is not affected with the disorder. When one parent is a carrier of a translocation, the chance of future offspring having Down syndrome is greatly increased. The specific risk will have to be assessed by a genetic counselor.

Demographics

Down syndrome occurs in about one in every 800 live births. It affects an equal number of male and female babies. The majority of cases of Down syndrome occur due to an extra chromosome 21 within the egg cell supplied by the mother (nondisjunction). As a woman's age (maternal age) increases, the risk of having a Down syndrome baby increases significantly. By the time the woman is age 35, the risk increases to one in 400; by age

40 the risk increases to one in 110; and, by age 45, the risk becomes one in 35. There is no increased risk of either mosaicism or translocation with increased maternal age.

Down syndrome occurs with equal frequency across all ethnic groups and subpopulations.

Signs and symptoms

While Down syndrome is a chromosomal disorder, a baby is usually identified at birth through observation of a set of common physical characteristics. Not all affected babies will exhibit all of the symptoms discussed. There is a large variability in the number and severity of these characteristics from one affected individual to the next. Babies with Down syndrome tend to be overly quiet, less responsive to stimuli, and have weak, floppy muscles. A number of physical signs may also be present. These include: a flat appearing face; a small head; a flat bridge of the nose; a smaller than normal, low-set nose; small mouth, which causes the tongue to stick out and to appear overly large; upward slanting eyes; bright speckles on the iris of the eye (Brushfield spots); extra folds of skin located at the inside corner of each eye and near the nose (epicanthal folds); rounded cheeks; small, misshapen ears; small, wide hands; an unusual deep crease across the center of the palm (simian crease); an inwardly curved little finger; a wide space between the great and the second toes; unusual creases on the soles of the feet; overly flexible joints (sometimes referred to as being double-jointed); and shorter-than-normal stature.

Other types of defects often accompany Down syndrome. Approximately 30–50% of all children with Down syndrome are found to have heart defects. A number of different heart defects are common in Down syndrome. All of these result in abnormal patterns of blood flow within the heart. Abnormal blood flow within the heart often means that less oxygen is sent into circulation throughout the body, which can cause fatigue, a lack of energy, and poor muscle tone.

Malformations of the gastrointestinal tract are present in about 5–7% of children with Down syndrome. The most common malformation is a narrowed, obstructed duodenum (the part of the intestine into which the stomach empties). This disorder, called duodenal atresia, interferes with the baby's milk or formula leaving the stomach and entering the intestine for digestion. The baby often vomits forcibly after feeding, and cannot gain weight appropriately until the defect is repaired.

Another malformation of the gastrointestinal tract seen in patients with Down syndrome is an abnormal connection between the windpipe (trachea) and the digestive tube of the throat (esophagus) called a tracheoesophageal fistula (T-E fistula). This connection interferes with eating and/or breathing because it allows air to enter the digestive system and/or food to enter the airway.

Other medical conditions occurring in patients with Down syndrome include an increased chance of developing infections, especially ear infections and pneumonia; certain kidney disorders; thyroid disease (especially low or hypothyroid); hearing loss; vision impairment requiring glasses (corrective lenses); and a 20 times greater chance than the population as a whole of developing leukemia.

Development in a baby and child affected with Down syndrome occurs at a much slower than normal

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Mental retardation—Significant impairment in intellectual function and adaptation in society. Usually associated an intelligence quotient (IQ) below 70.

Mosaic—A term referring to a genetic situation in which an individual's cells do not have the exact same composition of chromosomes. In Down syndrome, this may mean that some of the individual's cells have a normal 46 chromosomes, while other cells have an abnormal 47 chromosomes.

Nondisjunction—Non-separation of a chromosome pair, during either meiosis or mitosis.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

The sibling on the right has Down syndrome. *(Photo Researchers, Inc.)*

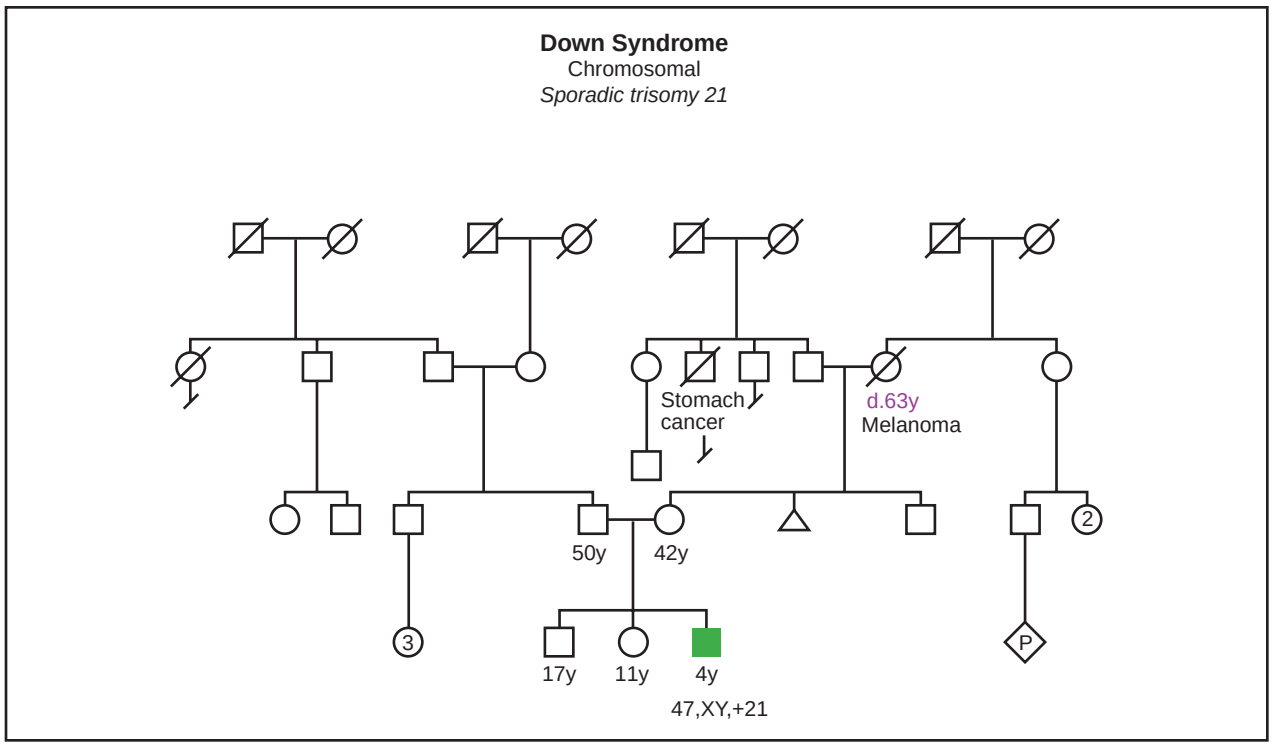
rate. Because of weak, floppy muscles (hypotonia), babies learn to sit up, crawl, and walk much later than their unaffected peers. Talking is also quite delayed. The level of mental retardation is considered to be mild-to-moderate in Down syndrome. The degree of mental retardation varies a great deal from one child to the next. While it is impossible to predict the severity of Down syndrome at birth, with proper education, children who have Down syndrome are capable of learning. Most children affected with Down syndrome can read and write and are placed in special education classes in school. The majority of individuals with Down syndrome become semi-independent adults, meaning that they can take care of their own needs with some assistance.

As people with Down syndrome age, they face an increased chance of developing the brain disease called Alzheimer's (sometimes referred to as **dementia** or senility). Most people have a 12% chance of developing **Alzheimer disease**, but almost all people with Down syndrome will have either Alzheimer disease or a similar type of dementia by the age of 50. Alzheimer disease causes the brain to shrink and to break down. The number of brain cells decreases, and abnormal deposits and structural arrangements occur. This process results in a loss of brain functioning. People with Alzheimer's have strikingly faulty memories. Over time, people with Alzheimer disease will lapse into an increasingly unresponsive state.

As people with Down syndrome age, they also have an increased chance of developing a number of other illnesses, including cataracts, thyroid problems, diabetes, and seizure disorders.

Diagnosis

Diagnosis is usually suspected at birth, when the characteristic physical signs of Down syndrome are noted. Once this suspicion has been raised, **genetic testing** (chromosome analysis) can be undertaken in order to verify the presence of the disorder. This testing is usually done on a blood sample, although chromosome analysis can also be done on other types of tissue, including the skin. The cells to be studied are prepared in a laboratory. Chemical stain is added to make the characteristics of the cells and the chromosomes stand out. Chemicals are added to prompt the cells to go through normal development, up to the point where the chromosomes are most visible, prior to cell division. At this point, they are examined under a microscope and photographed. The photograph is used to sort the different sizes and shapes of



(Gale Group)

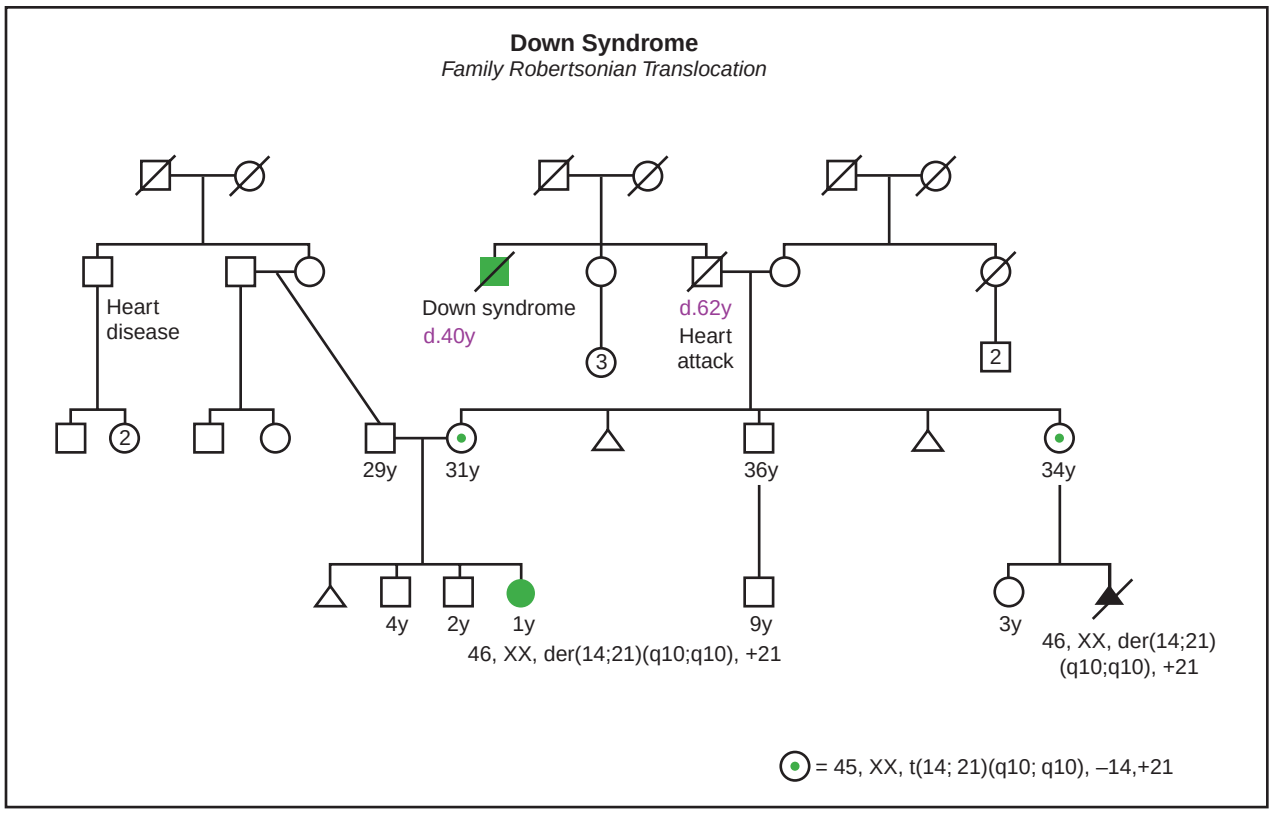
chromosomes into pairs. In most cases of Down syndrome, one extra chromosome 21 will be revealed. The final result of such testing, with the photographed chromosomes paired and organized by shape and size, is called the individual's **karyotype**. An individual with Down syndrome will have a 47 XX+21 karyotype if they are female and a 47 XY+21 karyotype if they are male.

Women who become pregnant after the age of 35 are offered prenatal tests to determine whether or not their developing baby is affected with Down syndrome. A genetic counselor meets with these families to inform them of the risks and to discuss the types of tests available to make a diagnosis prior to delivery. Because there is a slight risk of miscarriage following some prenatal tests, all testing is optional, and couples need to decide whether or not they desire to take this risk in order to learn the status of their unborn baby.

Screening tests are used to estimate the chance that an individual woman will have a baby with Down syndrome. A test called the maternal serum alpha-fetoprotein test (MSAFP) is offered to all pregnant women under the age of 35. If the mother decides to have this test, it is performed between 15 and 22 weeks of pregnancy. The MSAFP screen measures a protein and two hormones that are normally found in maternal blood during pregnancy. A specific pattern of these hormones and protein can indicate an increased risk for having a baby born with Down syndrome. However, this is only a risk and MSAFP cannot diagnose Down syndrome directly. Women found to have an increased risk of their babies being affected with Down syndrome are offered **amniocentesis**. The MSAFP test can detect up to 60% of all babies who will be born with Down syndrome.

Ultrasound screening for Down syndrome is also available. This is generally performed in the midtrimester of pregnancy. Abnormal growth patterns characteristic of Down syndrome such as growth retardation, heart defects, duodenal atresia, T-E fistula, shorter than normal long-bone lengths, and extra folds of skin along the back of the neck of the developing fetus may all be observed via ultrasonic imaging.

The only way to definitively establish (with about 99% accuracy) the presence or absence of Down syndrome in a developing baby is to test tissue during the pregnancy itself. This is usually done either by amniocentesis, or chorionic villus sampling (CVS). All women under the age of 35 who show a high risk for having a baby affected with Down syndrome via an MSAFP screen and all mothers over the age of 35 are offered either CVS or amniocentesis. In CVS, a tiny tube is inserted into the opening of the uterus to retrieve a small sample of the placenta (the organ that attaches the growing baby to the mother via the umbilical cord, and provides oxygen and nutrition). In amniocentesis, a small



(Gale Group)

amount of the fluid in which the baby is floating is withdrawn with a long, thin needle. CVS may be performed as early as 10 to 12 weeks into a pregnancy. Amniocentesis is generally not performed until at least the fifteenth week. Both CVS and amniocentesis carry small risks of miscarriage. Approximately 1% of women miscarry after undergoing CVS testing, while approximately one-half of one percent miscarry after undergoing amniocentesis. Both amniocentesis and CVS allow the baby's own karyotype to be determined.

Approximately 75% of all babies diagnosed prenatally as affected with Down syndrome do not survive to term and spontaneously miscarry. In addition, these prenatal tests can only diagnose Down syndrome, not the severity of the symptoms that the unborn child will experience. For this reason, a couple might use this information to begin to prepare for the arrival of a baby with Down syndrome, to terminate the pregnancy, or in the case of miscarriage or termination, decide whether to consider adoption as an alternative.

Treatment and management

No treatment is available to cure Down syndrome. Treatment is directed at addressing the individual concerns of a particular patient. For example, heart defects may require surgical repair, as will duodenal atresia and T-E fistula. Many Down syndrome patients will need to wear glasses to correct vision. Patients with hearing impairment benefit from hearing aids.

While some decades ago all children with Down syndrome were quickly placed into institutions for lifelong care, research shows very clearly that the best outlook for children with Down syndrome is a normal family life in their own home. This requires careful support and education of the parents and the siblings. It is a life-changing event to learn that a new baby has a permanent condition that will affect essentially all aspects of his or her development. Some community groups help families deal with the emotional effects of raising a child with Down syndrome. Schools are required to provide services to children with Down syndrome, sometimes in separate special education classrooms, and sometimes in regular classrooms (this is called mainstreaming or inclusion).

As of May 2000, the genetic sequence for chromosome 21 was fully determined, which opens the door to new approaches to the treatment of Down syndrome through the development of gene-specific therapies.

Prognosis

The prognosis for an individual with Down syndrome is quite variable, depending on the types of complications (heart defects, susceptibility to infections, development of leukemia, etc.). The severity of the retardation can also vary significantly. Without the presence of heart defects, about 90% of children with Down syndrome live into their teens. People with Down syndrome appear to go through the normal physical changes of aging more rapidly, however. The average age of death for an individual with Down syndrome is about 50 to 55 years.

Still, the prognosis for a baby born with Down syndrome is better than ever before. Because of modern medical treatments, including antibiotics to treat infections, and surgery to treat heart defects and duodenal atresia, life expectancy has greatly increased. Community and family support allows people with Down syndrome to have rich, meaningful relationships. Because of educational programs, some people with Down syndrome are able to hold jobs.

As of early 2001, there has only been one report of a male affected with Down syndrome becoming a father. Approximately 60% of women with Down syndrome are fully capable of having children. The risk of a woman with trisomy 21 having a child affected with Down syndrome is 50%.

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ORGANIZATIONS

National Down Syndrome Congress. 7000 Peachtree-Dunwoody Rd., Bldg 5, Suite 100, Atlanta, GA 30328-1662. (770) 604-9500 or (800) 232-6372. Fax: (770) 604-9898. ndsccenter@aol.com. <http://www.ndsccenter.org>.

National Down Syndrome Society. 666 Broadway, New York, NY 10012-2317. (212) 460-9330 or (800) 221-4602. Fax: (212) 979-2873. <http://www.ndss.org info@ndss.org>.

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Paul A. Johnson

DRPLA *see* **Dentatorubral-pallidoluysian atrophy**

Duane retraction syndrome

Definition

Duane retraction syndrome is a congenital disorder that limits the movement of the eye. It may also involve other systems of the body.

Description

Duane retraction syndrome (DRS or DURS) is an inherited disorder characterized by a limited ability to move the eye to one side or the other. DRS is congenital, meaning that it is present at birth. It results from abnormal connections among the nerves that control the muscles of the eyes. About 80% of DRS cases involve one eye (unilateral) and about 20% involve both eyes (bilateral). Most unilateral DRS cases (72%) involve the left eye.

DRS was first described in 1905 by A. Duane. It also is known as:

- Duane syndrome (DUS)
- DR syndrome
- eye retraction syndrome
- retraction syndrome
- Stilling-Turk-Duane syndrome

DRS is one of a group of conditions known as strabismus, or misalignment of the eye. DRS is classified as an incomitant strabismus, because it is a misalignment of

the eye that varies depending on the direction that the eye is gazing. It is further classified as an extraocular muscle fibrosis syndrome. This means that it is a condition associated with the muscles that move the eyes. Both the active and the passive movement of the eyeball are affected in DRS.

Physiology

DRS is believed to result from an abnormality that occurs during the development of the fetus in the womb. It may be caused by either environmental or genetic factors, or a combination of both. The developmental abnormality is believed to occur between the third and eighth weeks of fetal development. This is the period when the ocular muscles that rotate the eye, and the cranial nerves from the brain that control the ocular muscles, are forming in the fetus.

DRS appears to result from the absence of cranial nerve VI, which is known as the abducens nerve. The nerve cells in the brain that connect to the abducens nerve are also missing. The abducens nerve controls the lateral rectus muscle of the eye. This muscle moves one eye outward toward the ear, as a person looks toward that side. This movement is called abduction. In DRS, the nerves from a branch of cranial nerve III (the oculomotor nerve) also are abnormal. The oculomotor nerve controls several eye muscles, including the medial rectus muscle. This muscle moves the eye inward toward the nose, as the person looks toward the other side. This movement is called adduction.

The majority of individuals with DRS have limited or no ability to move an eye outward toward the ear. Instead, the opening between the eyelids of that eye widens and the eyeball protrudes. In addition, individuals with DRS may have only a limited ability to move the eye inward, toward the nose. Instead, when looking inward toward the nose, the medial and lateral recti muscles contract simultaneously. This causes the eyeball to retract, or pull into the skull, and causes the opening between the eyelids to narrow, as if one were squinting. Sometimes, the eye moves up or down as the individual attempts to look in toward the nose. This is called upshoot or downshoot, respectively.

In some individuals with DRS, the eyes may cross when looking straight ahead. Gazing straight ahead is called the primary position or primary gaze. Crossed eyes may cause the person to turn the head to one side or the other, to restore binocular vision. In such individuals, this "head turn" may become habitual.

Associated syndromes

About 30-50% of individuals with DRS have associated abnormalities. These may include additional eye problems, deafness, and nervous system or skeletal abnormalities. In particular, DRS may be associated with abnormalities in the upper extremities, especially the hands. Sometimes DRS is associated with **Holt-Oram syndrome**, a hereditary heart defect.

Okihiro syndrome is DRS in association with other abnormalities that may include:

- flatness in the normally-fleshy region between the thumb and the wrist (the thenar eminence) of one or both hands
- inability to flex the joint in the thumb
- hearing loss or deafness in one or both ears

Okihiro syndrome also is known as:

- Duane syndrome with radial ray anomalies (as in the arms and hands)
- Duane/radial **dysplasia** syndrome (referring to abnormal tissue growth in the arms and hands)
- DR syndrome (the "D" refers to Duane anomaly and deafness; the "R" refers to radial and renal (kidney) dysplasia, or abnormal tissue growth in the arms, hands, and kidneys)
- Duane anomaly with radial ray abnormalities and deafness

Genetic profile

The genetic basis of DRS is unclear. The specific **gene** or genes that are responsible for DRS and the associated syndromes have not been identified. DRS may arise from a combination of environmental factors and defects in one or more genes.

Portions of several of the 23 pairs of human **chromosomes** may be associated with DRS. A gene that is involved in DRS has been localized to a region of chromosome 2. Deletions of portions of chromosomes 4 and 8 have also been associated with DRS. The presence of an additional small chromosome, thought to be broken off from chromosome 22, has been associated with DRS. It is possible that these chromosome rearrangements and abnormalities may account for the wide range of symptoms and syndromes that can occur with DRS.

The **inheritance** of DRS is autosomal, meaning that the trait is not carried on either the X or Y sex chromosomes. The most common type of DRS, DRS1, is inherited as an autosomal dominant trait. This means that only a single copy of a DRS gene, inherited from one parent, can result in the condition. The offspring of a parent with DRS is expected to have a 50% chance of inheriting the disorder. However, the autosomal dominant form of DRS sometimes skips a generation in the affected family; for example, a grandparent and grandchildren may have

DRS, but the middle generation does not. Some forms of DRS may be recessive, requiring two copies of a gene, one inherited from each parent.

Family members may exhibit different types of DRS, indicating that the same genetic defect may be expressed by a range of symptoms. The severity of DRS also may vary among family members. Furthermore, the majority of individuals with DRS do not appear to have a family history of the disorder. There are very few reports of single families with a large number of affected individuals. However, close relatives of individuals with DRS often are affected by some of the other abnormalities that may be associated with the disorder.

Okihiro syndrome, or Duane syndrome with radial ray anomalies, and Holt-Oram syndrome both are inherited as autosomal dominant traits. However, like DRS, Okihiro syndrome may skip a generation in a family, or may be expressed by a range of symptoms within one family.

Demographics

DRS is estimated to affect 0.1% of the general population. It accounts for 1-5% of all eye movement disorders. Although it is not a sex-linked disorder, females are more likely than males to be affected by DRS (60% compared with 40%).

Signs and symptoms

Types of DRS

There are three generally-recognized types of DRS. Type 1 DRS (DRS1) accounts for about 70% of cases. With DRS1, abduction, the ability to move the eye toward the ear, is limited or absent. The eye widens and the eyeball protrudes when the eye is moved outward. In contrast, adduction, the ability to move the eye toward the nose, is normal or almost normal. However, the eye narrows and the eyeball retracts during adduction. The eyes of infants and children with DRS1 are usually straight ahead in the primary position. However, some children develop an increasing misalignment in the primary position and may compensate by turning their head.

With DRS type 2, adduction is limited or absent but abduction is normal, or only slightly limited. The eye narrows and the eyeball retracts during adduction. Type 2 accounts for approximately 7% of DRS cases.

With DRS Type 3, both abduction and adduction are limited. The eye narrows and the eyeball retracts during adduction. Type 3 accounts for about 15% of DRS cases.

Each type of DRS is subclassified, depending on the symptoms that occur when the individual is looking

KEY TERMS

Abducens nerve—Cranial nerve VI; the nerve that extends from the midbrain to the lateral rectus muscle of the eye and controls movement of the eye toward the ear (abduction).

Abduction—Turning away from the body.

Adduction—Movement toward the body. In Duane retraction syndrome, turning the eye inward toward the nose.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Congenital—Refers to a disorder which is present at birth.

Downshoot—Downward movement of the eye.

Dysplasia—The abnormal growth or development of a tissue or organ.

Extraocular muscle fibrosis—Abnormalities in the muscles that control eye movement.

Head turn—Habitual head position that has been adopted to compensate for abnormal eye movements.

Holt-Oram syndrome—Inherited disorder characterized by congenital heart defects and abnormalities of the arms and hands; may be associated with Duane retraction syndrome.

Lateral rectus muscle—The muscle that turns the eye outward toward the ear (abduction).

Medial rectus muscle—The muscle that turns the eye inward toward the nose (adduction).

Oculomotor nerve—Cranial nerve III; the nerve that extends from the midbrain to several of the muscles that control eye movement.

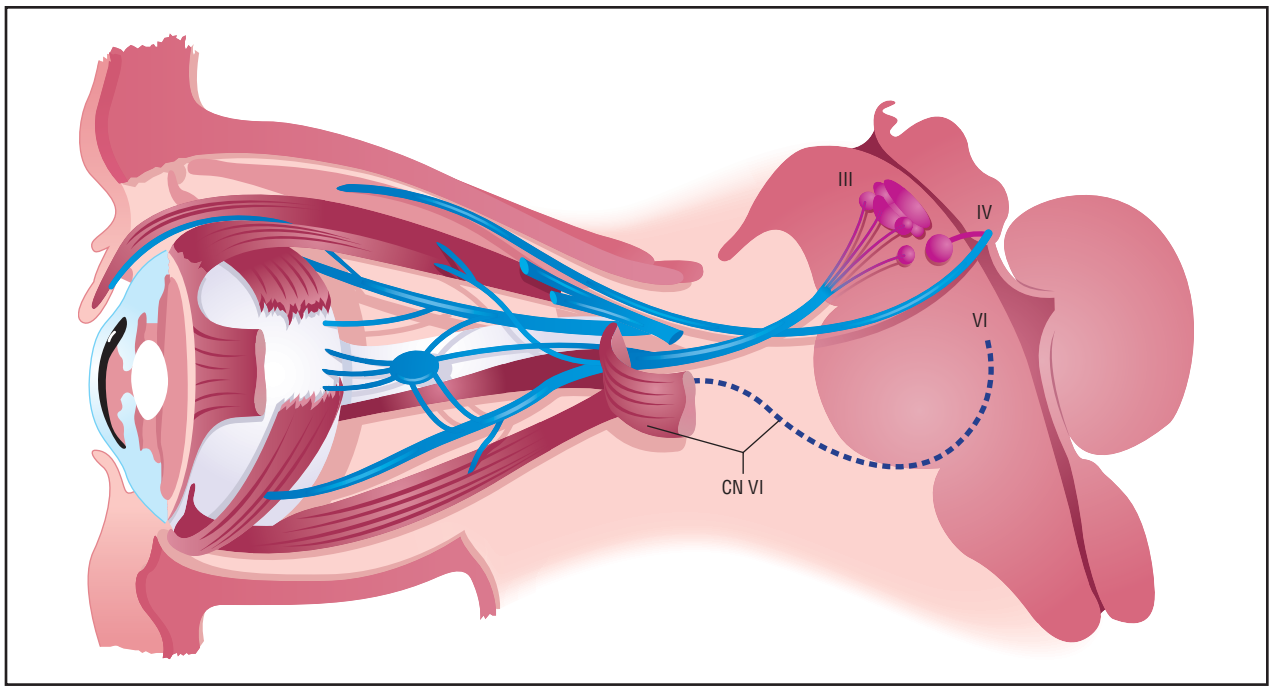
Okihiro syndrome—Inherited disorder characterized by abnormalities of the hands and arms and hearing loss; may be associated with Duane retraction syndrome.

Primary position, primary gaze—When both eyes are looking straight ahead.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

Strabismus—An improper muscle balance of the ocular musles resulting in crossed or divergent eyes.

Upshoot—Upward movement of the eye.



Absence of cranial nerve VI (dashed line) is indicative of Duane retraction syndrome and results in abnormal head and eye movements. *(Gale Group)*

straight ahead (primary gaze). With subgroup A, the eye turns in toward the nose when gazing ahead. With subgroup B, the eye turns out toward the ear during a primary gaze. With subgroup C, the eyes are straight ahead in the primary position.

Associated symptoms

The majority of individuals with DRS are healthy and have no other symptoms. However, other body systems that may be affected with DRS include:

- skeleton
- ears and hearing
- additional involvement of the eyes
- nervous system

With Okihiro syndrome, the DRS can be unilateral or bilateral. In addition to a flatness at the base of the thumb, there may be difficulty with thumb movements. There also may be abnormalities or the complete absence of the radial and ulnar bones of the forearm. In extreme cases, the thumb or forearm may be absent. Okihiro syndrome may be accompanied by hearing loss, abnormal facial appearance, and heart, kidney, and spinal abnormalities.

Sometimes Wildervanck syndrome is associated with DRS. This syndrome may include congenital deafness and a fusion of the cervical (neck) vertebrae (C2 and C3).

Diagnosis

Diagnosis of DRS usually occurs by the age of ten. The clinical evaluation includes a complete family history, an eye examination, and examinations for other eye involvement or other physical abnormalities.

Eye examinations include the following measurements:

- visual acuity or sharpness
- alignment of the eyes
- range of motion of the eyes
- retraction (pulling in) of the eyeballs
- size of the eye opening between the eyelids
- upshoots and downshoots
- head turns

Hearing tests are frequently conducted. The cervical (neck) and thoracic (chest) parts of the spine, the vertebrae, the hands, and the roof of the mouth all are included in the examination as well.

Treatment and management

Special glasses with prisms can eliminate the head turning that is associated with DRS. Vision therapy may help with secondary vision problems.

Surgery may be performed for the following cosmetic reasons:

- abnormalities in the primary gaze (when looking straight ahead)
- an unusual compensatory head position
- a large upshoot or downshoot
- severe retraction of the eye

The goal of surgery is to reduce or eliminate the misalignment of the eye that causes abnormal head turning, as well as to reduce the retraction of the eyeball and the upshoots and downshoots. The surgery is directed at the affected muscles of the eye.

Children with DRS, as well as their siblings, require complete medical examinations to detect other abnormalities that may be associated with DRS.

Prognosis

If children with DRS go undiagnosed, a permanent loss of vision may occur. Surgical procedures may eliminate head turns and improve the misalignment of the eyes, particularly in the primary position. However, the absence of nerves for controlling the muscles of the eye cannot be corrected. Thus, no surgical procedure can completely eliminate the abnormal eye movements. However, the condition does not get worse during the course of one's life.

Resources

BOOKS

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ORGANIZATIONS

American Association for Pediatric Ophthalmology and Strabismus. <http://med-aapos.bu.edu/>.

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937. info@geneticalliance. <http://www.geneticalliance.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637 or (914) 428-7100. resourcecenter@modimes.org. <http://www.modimes.org>.

National Eye Institute. National Institutes of Health. 31 Center Dr., Bldg. 31, Rm 6A32, MSC 2510, Bethesda, MD 20892-2510. (301) 496-5248. 2020@nei.nih.gov. <http://www.nei.nih.gov/>.

Schepens Eye Research Institute. 20 Staniford St., Boston, MA 02114-2500. (617) 912-0100. <http://www.eri.harvard.edu>.

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Margaret Alic, PhD

Dubowitz syndrome

Definition

Dubowitz syndrome is a genetic disorder defined by slow growth, a characteristic facial appearance, and a small head.

Description

Dubowitz syndrome was first described in 1965 by the English physician Dr. Victor Dubowitz. This genetic disorder causes growth retardation both before and after birth. It is primarily diagnosed through the distinctive facial features of affected individuals, including a small triangular-shaped face with a high forehead and wide-set, slitted eyes. A number of other symptoms, most commonly irritation and itching of the skin (eczema), may be present in infants born with Dubowitz syndrome.

Genetic profile

Dubowitz syndrome is passed on through an autosomal recessive pattern of **inheritance**. Autosomal means that the syndrome is not carried on a sex chromosome, while recessive means that both parents must carry the

KEY TERMS

Eczema—Inflammation of the skin with redness and other variable signs such as crusts, watery discharge, itching.

Microcephaly—An abnormally small head.

Ptosis—Drooping of the upper eyelid.

gene mutation in order for their child to have the disorder. Parents with one child affected by Dubowitz syndrome have a 25% chance that their next child will also be affected with the disease.

As of 2001, the specific **gene mutation** responsible for Dubowitz syndrome had not yet been identified.

Demographics

Cases of Dubowitz syndrome have been reported from many different regions of the world with the majority coming from the United States, Germany, and Russia. There does not appear to be any clear-cut ethnic pattern to the incidence of the syndrome. Dubowitz syndrome appears to affect males and females with equal probability. The overall incidence of the disorder has not been established since it is very rare. As of 1996, only 141 cases had been reported worldwide.

Signs and symptoms

Physical characteristics

The symptoms of people diagnosed with Dubowitz syndrome vary considerably. However, the most common physical characteristics associated with Dubowitz syndrome are growth retardation, characteristic facial appearance, and a very small head (microcephaly). A wide variety of secondary physical characteristics may be present.

GROWTH RETARDATION Children born with Dubowitz syndrome usually have a low birth weight. Slower than normal growth continues after birth. Even if the infant is born in the normal range, the height and weight gradually falls toward the low end of growth curves during childhood. However, Dubowitz syndrome is not a form of dwarfism, because affected individuals have normally proportioned bodies.

FACIAL APPEARANCE The characteristic facial appearance of people with Dubowitz syndrome is the primary way in which the disorder is recognized. The face is small and often triangular in shape with a pointed, receding chin. The nose is broad with a wide or rounded tip. The eyes are set far apart and sometimes appear slitted due to a decreased distance between top and bottom eyelids or a drooping top eyelid. The forehead is high, broad, and sloping. Eyebrows and hair are thin or absent. The ears may be abnormally shaped or placed.

MICROCEPHALY Infants born with Dubowitz syndrome have primary microcephaly, or a small head size at birth. By definition, in microcephaly the circumference of the head is in the second percentile or less, meaning that 98% or more of all infants have a larger head circumference than an infant with microcephaly.

OTHER PHYSICAL CHARACTERISTICS There are many other physical characteristics that have been observed in the majority of cases of Dubowitz syndrome, although they are not present in all affected individuals. These include:

- A soft or high-pitched cry or voice
- Partial webbing of the toes
- Cleft palate or less severe palate malformations
- Genital abnormalities, including undescended testicles
- Gastroesophophageal reflux
- Inflammation and itching of the skin (eczema)

Mental and behavioral characteristics

Despite the small head size of children born with Dubowitz syndrome, developmental delay is not observed in all cases. Estimates of the incidence of developmental delay in cases of Dubowitz syndrome range from 30% to 70%, and in most cases the level of the mental retardation is rather mild.

A number of behavioral characteristics have been described by parents of children with Dubowitz syndrome as well as in the medical literature. These include:

- Extreme hyperactivity
- Temper tantrums, difficulty in self-calming
- Preference for concrete thinking rather than abstract thinking
- Language difficulties
- Shyness and aversion to crowds
- Fondness for music and rhythm

Diagnosis

Since the genetic cause is not known, there is no specific medical test that can definitively assign the diagno-

sis of Dubowitz syndrome. The diagnosis is usually based on the characteristic facial appearance of the affected individual as well as on other factors such as growth data and medical history. The diagnosis is easily missed if the physician is not familiar with genetic pediatric conditions.

Treatment and management

A number of chronic medical conditions are associated with Dubowitz syndrome. These include:

- Inflammation and itching of the skin (eczema)
- Susceptibility to viral infections
- Allergies
- Chronic diarrhea or constipation
- Feeding difficulties and vomiting

These conditions need to be managed individually with appropriate treatments. For example, skin creams containing corticosteroid drugs are used to treat eczema.

Other physical problems caused by Dubowitz syndrome, such as drooping eyelids (ptosis) or cardiovascular defects, can be corrected through surgery.

Prognosis

The prognosis for individuals affected by Dubowitz syndrome is good provided that management of their medical conditions is maintained. Dubowitz syndrome has not been reported to cause shortened lifespan or any degenerative conditions. People with Dubowitz syndrome can expect to survive to adulthood and lead a fairly normal lifestyle, although most have some level of mental retardation.

Resources

PERIODICALS

Tsukahara, M., and J. Opitz. "Dubowitz Syndrome: Review of 141 Cases Including 36 Previously Unreported Patients." *American Journal of Human Genetics* (1996): 277-289.

ORGANIZATIONS

Dubowitz Syndrome Nationwide Support Group Network. RR 1 Box 114, Downs, IL 61736. (309) 724-8407.

Dubowitz Syndrome Parent Support. PO Box 173, Wheatland, IN 47597. (812) 886-0575.

WEBSITES

Dubowitz Syndrome Information and Parent Support. <http://www.dubowitz.org/> (20 April 2001).

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Paul A. Johnson

Duchenne muscular dystrophy

Definition

The group of conditions called muscular dystrophies are characterized by muscle weakness and degeneration. Duchenne is a relatively common, severe **muscular dystrophy**. Becker muscular dystrophy is less common and less severe. Becker and Duchenne muscular dystrophy were once considered to be separate conditions. In the 1990s, researchers showed that Duchenne and Becker muscular dystrophy have the same etiology (underlying cause). However, the two disorders remain distinct based on different ages on onset, rates of progression, and some distinct symptoms.

Description

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are both defined by progressive muscle weakness and atrophy. Both conditions are caused by a mutation in the same **gene** and usually affect only boys. Symptoms of Duchenne muscular dystrophy usually begin in childhood, and boys with DMD are often in wheelchairs by the age of 12 years. Symptoms of Becker muscular dystrophy begin later, and men with BMD typically do not require wheelchairs until their 20s.

Boys with Duchenne muscular dystrophy are usually diagnosed at a young age. Boys with Becker muscular dystrophy are often diagnosed much later. Both conditions are progressive, although DMD progresses more quickly than BMD. Unfortunately, no treatments exist to slow or prevent progression of the disease. Skeletal muscles are affected initially. Eventually the muscles of the heart are also affected, and both conditions are fatal. The life expectancy of males with Duchenne and Becker is 18 years and approximately 45 years, respectively. Both conditions are caused by disorders of the muscle, not of the nerves that control the muscle.

Genetic profile

Duchenne and Becker muscular dystrophy are both caused by mutations in the *DMD* gene on the X chromosome. This is an exceptionally large gene, and control of its expression is complex.

Humans each have 46 **chromosomes**, of which 23 are inherited from the mother and 23 are inherited from the father. The sets of 23 chromosomes are complimentary: each contains the same set of genes. Therefore, every human has a pair of every gene. Genes are the sequences of **DNA** that encode instructions for growth,

development, and functioning. One of the 23 pairs of chromosomes may not be complimentary: the sex chromosomes. Boys have an X chromosome and a Y chromosome. Girls have two X chromosomes.

Scientists often say that every person has the same genes, and that the genes on a pair of complimentary chromosomes are the same. It is true that a specific gene at a specific place on each chromosome provides the body with a very specific instruction, i.e. plays a particular functional role. However, most genes have multiple forms. Scientists call the various forms of a gene *alleles*. A given gene may have multiple alleles that function normally and multiple alleles that lead to physical problems.

Mutations (changes) in the DMD gene cause Duchenne and Becker muscular dystrophy. The DMD gene provides instructions for a protein called dystrophin. Mutations in DMD associated with Duchenne often completely disrupt production of dystrophin, such that no dystrophin is present. Mutations in DMD associated with Becker lead to a reduced amount of dystrophin being made and/or abnormal dystrophin. Certain mutations (alleles) in the DMD gene lead to the symptoms of DMD and other mutations lead to the symptoms of BMD.

Sex linked inheritance

Because the DMD gene is on the X chromosome, Duchenne and Becker muscular dystrophy affect only boys. Most females have two X chromosomes. Thus, if a female inherits an X chromosome with a mutation in the DMD gene, she has another normal DMD gene on her other X chromosome that protects her from developing symptoms. Women who have one mutated gene and one normal gene are called carriers. Boys, on the other hand, have an X and a Y chromosome. The Y chromosome has a different set of genes than the X chromosome; it mostly contains genes that provide instructions for male development. If a boy has a mutation in the DMD gene on his X chromosome, he has no normal DMD gene and he has muscular dystrophy.

If a woman has one son with Duchenne or Becker and no other family history, she may or may not be a carrier. If a woman has another family member with Duchenne or Becker muscular dystrophy, *and* a son with muscular dystrophy, it is assumed that she is a carrier. The risk for a male child to inherit the mutated gene from his carrier mother is 50% with each pregnancy. Based on the family history, geneticists can determine the likelihood that a woman is or is not a carrier. Based on this estimate, risks to have a son with muscular dystrophy can be provided.

New mutations

The DMD gene is very large and new mutations are fairly common. A new mutation is a mutation that occurs for the first time, that no other members have. Approximately 1/3 of males with Duchenne who have no family history of muscular dystrophy have the condition because of a new mutation that is only present in themselves. In this case, the affected male's mother is not a carrier. Approximately 2/3 of males with Duchenne and no family history have it because of a new mutation that occurred in a relative. In other words, even if the affected male is the first in his family his mother may still be carrier. The new mutation could have happened for the first time in the affected male's mother, or the new mutation could have occurred in his maternal grandmother or grandfather (or their parents, or their parents, etc.).

Sometimes a woman or man has mutations in the DMD gene of his or her sperm or eggs, but not in the other cells of his or her body. The mutation may even be in some sperm and/or eggs but not in others. This situation is called "germline mosaicism". Germline cells are the egg and sperm cells. A woman or man with germline mosaicism may have more than one affected son even though genetic studies of his or her blood show that he or she is not a carrier. Geneticists can estimate the risk that a person has germline mosaicism, and provide information regarding the risk for a person with germline mosaicism to have a child with muscular dystrophy.

Demographics

Duchenne muscular dystrophy affects approximately 1/3,500 males. Males from every ethnicity are affected. Becker muscular dystrophy is much less common than Duchenne muscular dystrophy. The incidence of Becker muscular dystrophy is approximately 1/18,000.

Signs and symptoms

Both Becker and Duchenne muscular dystrophy initially affect skeletal muscle. Muscle weakness is the first symptom. Both conditions are progressive. Duchenne progresses more rapidly than Becker. People with Duchenne usually begin to use a wheelchair in their early teens, while people with Becker muscular dystrophy may not use a wheelchair until their twenties or later. In the late stages of both diseases, the cardiac muscles begin to be affected. Impairment of the heart and cardiac muscles leads to death. Some female carriers have mild muscle weakness.

People with muscular dystrophy often develop contractures. A contracture makes a joint difficult to move. The joint becomes frozen in place, sometimes in a

painful position. **Scoliosis** (curvature of the spine) is another common problem. Most people with Duchenne have normal intelligence, but cognition is affected in some. Cognition is not usually affected in Becker muscular dystrophy.

Dystrophin

The DMD gene contains instructions for a protein called dystrophin. Dystrophin is part of muscle cells and some nerve cells. Its function is not entirely understood. Based on its location in the muscle cell, scientists think that dystrophin may help maintain the structural integrity of muscle cells as they contract. People with Duchenne make very little or no dystrophin, and people with Becker make less than normal and/or semi-functional dystophin. When there is not enough dystrophin in the muscle, it becomes weak and starts to waste away. The muscle tissue is replaced by a fatty, fibrous tissue.

Duchenne muscular dystrophy

The first symptoms of Duchenne muscular dystrophy are usually noticed in early childhood. Delays in developmental milestones, such as sitting and standing, are common. The affected child's gait is often a characteristic waddle or toe-walk. He often stumbles, and running is difficult. While parents notice these symptoms retrospectively, and may notice them at the time, muscular dystrophy often is not suspected until additional signs are apparent. By the age of four to five years, it is difficult for the child to climb stairs or rise from a sitting position on the floor. It is around this time that the diagnosis is usually made. A particular method, called the *Gower sign* is used by the child to raise himself from sitting on the floor. These motor problems are caused by weakness in large muscles close to the center of the body (proximal).

Although some muscles, such as the calves, appear to be large and defined, the muscle is actually atrophied and weak. It appears large because deposits of fatty, fibrous tissue are replacing muscle tissue. Enlarged calves are a characteristic sign of Duchenne muscular dystrophy, and are said have pseudohypertrophy. "Pseudo" means false, "hyper" is excessive, and " trophy" is growth or nourishment. Other muscles may also have pseudohypertophy. These muscles feel firm if massaged.

The weakness begins at the center of the body (the pelvis) and progresses outward from the hips and shoulders to the large muscles of the legs, lower trunk, and arms. The weakness is symmetrical; i.e. both sides of the body are equally weak. Early signs of weakness, such as stumbling and difficulty climbing, progress to the point that the affected boy is unable to walk. Boys with Duchenne muscular dystrophy usually require wheelchairs by the age of 12 years. Eventually the muscles that support the neck are affected. The muscles of the digestive tract are affected in some males in the later stages of the disease. Contractures and scoliosis develop. Some boys also have learning disabilities or mild mental retardation.

Cardiac symptoms and life expectancy

The weakness usually affects skeletal muscles first, then cardiac muscle. Skeletal muscles are those that attach to bones and produce movement. The muscle weakness of both Duchenne and Becker muscular dystrophy progresses to affect the cardiac muscles. Weak, abnormal cardiac muscles cause breathing difficulties

KEY TERMS

Cardiac muscle—The muscle of the heart.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Skeletal muscle—Muscles under voluntary control that attach to bone and control movement.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

X inactivation—Sometimes called "dosage compensation". A normal process in which one X chromosome in every cell of every female is permanently inactivated.

and heart problems. Breathing difficulties lead to lung infections, such as pneumonia. These problems are fatal in Duchenne, and often fatal in Becker. The life expectancy for a boy with Duchenne muscular dystrophy is the late teens or early twenties. The average life expectancy of males with Becker muscular dystrophy is the mid-forties.

Becker muscular dystrophy

The initial signs of Becker muscular dystrophy may be subtle. The age at which symptoms become apparent is later and more variable than that of DMD. The progression of Becker muscular dystrophy is slower than that of DMD. Like Duchenne muscular dystrophy, boys with BMD develop symmetrical weakness of proximal muscles. The calf muscles often appear especially large. Boys with Duchenne muscular dystrophy develop weakness in the muscles that support their necks, but boys with BMD do not. The incidence and severity of learning disabilities and mild mental retardation is less in Becker muscular dystrophy than in Duchenne.

The first symptoms of Becker muscular dystrophy usually appear in the twenties and may appear even later. Weakness of the quadriceps (thigh muscle) or cramping with exercise may be the first symptom. The age of onset and rate of progression are influenced by how much dystrophin is made and how well it functions. Not all males with Becker muscular dystrophy become confined to wheelchairs. If they are, the age at which they begin to use the wheelchair is later than in Duchenne. Many males with Becker muscular dystrophy are ambulatory in their twenties. However, many males with Becker eventually develop cardiac problems, even if they do not have a great deal of skeletal muscle weakness. Cardiac problems are typically fatal by the mid-40s. Some men with Becker muscular dystrophy remain ambulatory (and alive) into their sixties.

Since Duchenne and Becker muscular dystrophy are caused by a mutation (change) in the same gene, the two conditions are usually distinguished based on age of onset and rate of progression. Males with Duchenne usually require wheelchairs by the age of 12 years and males with Becker usually do not require wheelchairs until after the age of 16. However, some males with muscular dystrophy develop symptoms at an intermediate age. Similarly, some males have elevated creatine kinase and abnormal muscle biopsies but do not develop most of the symptoms typical of muscular dystrophy. Some doctors would classify these males with very mild symptoms as having “mild Becker muscular dystrophy”. Some individuals who have Becker muscular dystrophy with mildly affected skeletal muscles still develop abnormalities of their cardiac muscle.

Many other forms of muscular dystrophy exist and are part of the diagnoses considered when a person develops signs of Duchenne or Becker muscular dystrophy. The symptoms of Becker muscular dystrophy, in particular, may be caused by many other conditions. However, diagnostic studies can definitively confirm whether an individual has Becker muscular dystrophy.

Affected females

It is unusual, but some females have some or all of the symptoms of muscular dystrophy. Assuming that the diagnosis is correct, this can happen for various reasons. If a woman has **Turner syndrome**, in which she has one X chromosome instead of two, she could also have Duchenne or Becker muscular dystrophy. (She has no second X chromosome with a normal DMD gene to protect her.) Alternatively, a woman may have muscular dystrophy because of random unfavorable “X inactivation”, or because she has a chromosomal translocation. Rarely, she may also have inherited both X chromosomes from the same parent.

Diagnosis

The diagnosis of muscular dystrophy is based on physical symptoms, family history, muscle biopsy, measurement of creatine kinase, and **genetic testing**. Creatine kinase (CK) may also be called creatine phosphokinase or CPK. It is a protein present in skeletal muscle, cardiac muscle, and the brain.

Creatine kinase is released into the blood as muscle cells die. The level of CK in the blood is increased if a person has muscular dystrophy. The level in a male with Duchenne is often more than ten times the normal level, and the level in a male with Becker is often at least five times more than the normal level. The level of CK in the blood of female carriers is variable. Approximately 50% of Duchenne muscular dystrophy carriers have slightly to greatly elevated serum creatine kinase. Only about 30% of carriers of Becker muscular dystrophy have elevated creatine kinase. Therefore, the measurement of creatine kinase is not an accurate predictor of carrier status.

If a muscle biopsy is performed, a small piece of muscle tissue is removed from the patient. Special studies are performed on the tissue. Early in the course of the disease, the muscle shows general abnormalities. Later in the disease, the muscle tissue appears more abnormal. The fat and fibrous tissues that are replacing the muscle fibers are visable.

Another specialized test of muscle function, the electromyogram (EMG) may be performed. The EMG records the electrical activity of a muscle. This test is used to determine whether the symptoms are the result of

an underlying muscle problem or a nerve problem. Nerves stimulate muscles to contract. A non-functioning muscle due to a nerve problem often causes the same symptoms as a non-functioning muscle caused by a problem with the muscle.

Genetic testing

Genetic testing is a useful diagnostic tool because the diagnosis can be made without an invasive muscle biopsy. Blood from the person suspected to have muscular dystrophy is analyzed at a specialty laboratory. Genetic testing will confirm that the DMD gene is abnormal in most males affected with muscular dystrophy (70% with DMD and 85% with BMD). The disease causing mutation will be unidentifiable in some males who have muscular dystrophy. Therefore, an abnormal test result is definitive, but a normal test result is not. In these cases, muscle biopsy may be necessary to confirm the diagnosis. Muscle biopsy may be helpful to determine whether a young person with mild symptoms has Duchenne or Becker even when the diagnosis of muscular dystrophy is established by genetic testing.

The severity of the mutation is correlated to the severity of the disease. For example, mutations that completely eliminate the dystrophin protein are associated with DMD much more often than they are associated with BMD. Particular mutations have been associated with intellectual impairment. The severity of symptoms can be somewhat predicted by the mutation present.

Even when a mutation in the DMD gene has been identified in the affected family member, genetic testing to determine whether or not the females are carriers may not be straightforward.

In some families, a special form of genetic testing called "linkage testing" may be helpful. Linkage genetic testing can be performed when the diagnosis of Duchenne or Becker muscular dystrophy is certain in more than one family member but no mutation is identified in the DMD gene. Linkage testing requires the participation of multiple family members. Unique DNA sequences within the gene and flanking the gene are analyzed to determine whether the sequences are those associated with the deleterious gene or with the normal gene. This method is not 100% accurate.

If a woman knows that she is a carrier, prenatal and preimplantation diagnosis are available. If the specific DMD or BMD mutation has been identified in a family member, genetic testing can be performed on the fetus. The procedures used to obtain fetal cells are chorionic villus sampling (CVS) and **amniocentesis**. CVS is usually performed between 10 and 12 weeks of pregnancy, and amniocentesis is usually performed after 16 weeks. Whether amniocentesis or CVS is performed, chromosomal analysis of the fetal cells will show whether the baby is male or female. Linkage testing may also be performed prenatally.

Treatment and management

There is no cure for muscular dystrophy. However, doctors are getting better at treating the symptoms. Many researchers are searching for preventative measures and for a cure. In 2001, therapies focus on treating the associated symptoms.

Preventative measures

Exercise and physical therapy help to prevent joint contractures and maintain mobility. Avoiding obesity is important. Orthopedic devices may delay the age at which an affected boy begins to use a wheelchair, and are often used to treat scoliosis. Motorized wheelchairs and other devices help an affected person who has become disabled to maintain his independence as long as possible. When the cardiac muscles become affected, respiratory care may be necessary. Cardiac function should be evaluated in adult males with Becker muscular dystrophy even when skeletal muscles are mildly affected. Some women who are carriers of Duchenne muscular dystrophy develop heart disease related to changes in their cardiac muscle. Therefore, surveillance for heart disease should be a consideration for women who are carriers of DMD.

Experimental therapies

Some researchers are trying to deliver normal dystrophin protein to the muscle. If this were done by **gene therapy**, a normal copy of the DMD gene would be inserted into the muscle cells. In 2001, neither gene therapy nor dystrophin protein replacement is available. In fact, this research is in the early stages. But the theoretical possibility gives researchers hope that in the future there may be a cure.

Researchers have also experimentally transferred healthy muscle cells into the tissue of individuals with muscular dystrophy. This is not a standard treatment as of 2001. However, it provides another hope that in the future an effective treatment will be developed.

Claims have been made that a class of medications called corticosteroids slows the progression of muscle destruction in muscular dystrophy. The use of these drugs is controversial. Corticosteroids have not been proven to have a long-term effect. Also, corticosteroids have many serious side effects. Cortisone is a corticosteroid, and prednisone is similar to cortisone.

Discovering the DMD gene allowed researchers to create animal models for muscular dystrophy. They have created mice and other animals that have Duchenne muscular dystrophy in order to more effectively study the disease and test the efficacy of treatments. This development also provides hope for the future.

Prognosis

The prognosis of Duchenne muscular dystrophy is confinement to a wheelchair by the age of 12 years, and usually death by the late teens or early twenties. The prognosis for Becker muscular dystrophy varies. Some individuals with BMD require a wheelchair after 16 years of age, but others remain ambulatory into middle adulthood. Some mildly affected individuals never require a wheelchair. The average life expectancy for Becker muscular dystrophy is the mid-forties. Both conditions are progressively debilitating.

Because Duchenne is a relatively common and severe condition, many people very actively promote further funding, research, and support of affected individuals. Associations to help families with muscular dystrophy have chapters all over the world. Families and researchers are hopeful that the genetic discoveries of the 1990s will lead to new treatments and cures in the next millennium. However, the obstacles between understanding the pathogenesis of a disease and creating an effective treatment are large. This is especially true of muscular dystrophy.

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Muscular Dystrophy Campaign. 7-11 Prescott Place, London, SW4 6BS. UK +44(0) 7720 8055. info@muscular-dystrophy.org. <http://www.muscular-dystrophy.org>.

Muscular Dystrophy Family Foundation. 615 North Alabama St., Ste. 330, Indianapolis, IN 46204-1213. (317) 632-8255 or (800) 544-1213. mdff@prodigy.net. <http://www.mdff.org>.

Parent Project for Muscular Dystrophy Research. 1012 N. University Blvd., Middletown, OH 45042. (413) 424-0696 or (800) 714-5437. parentproject@aol.com. <http://www.parentdmd.org>.

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Michelle Q. Bosworth, MS, CGC

Dwarfism *see* **Pituitary dwarfism syndrome**

Dysplasia

Definition

Dysplasia is a combination of two Greek words; *dys-*, which means difficult or disordered; and *plassein*, to form. In other words, dysplasia is the abnormal or disordered organization of cells into tissues. All abnormalities relating to abnormal tissue formation are classified as dysplasias.

Description

Tissues displaying abnormal cellular organization are called dysplastic. Dysplasias may occur as the result of any number of stimuli. Additionally dysplasia may occur as a localized or a generalized abnormality. In a localized dysplasia, the tissue abnormality is confined to the tissue in a single area, or body part. In a generalized dysplasia, the abnormal tissue is an original defect leading to structural consequences in different body parts.

Localized dysplasia

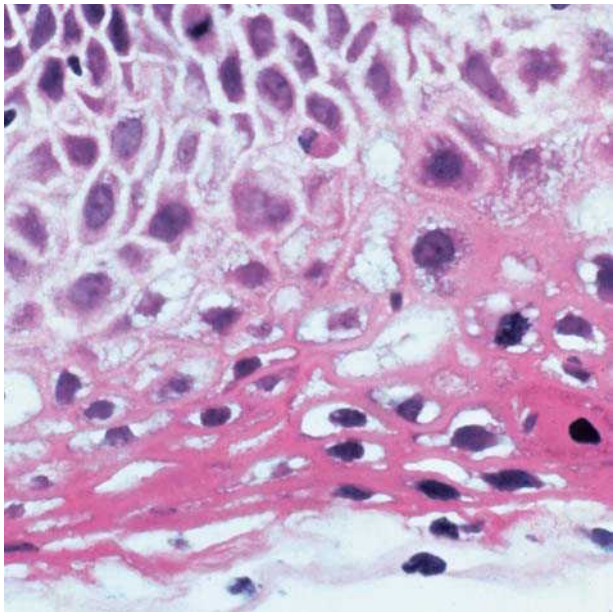
Localized dysplasia may occur as the result of any number of stimuli and affect virtually any organ. Stimuli leading to localized dysplasia may include viruses, chemicals, mechanical irritation, fire, or even sunlight. Sunburned skin, for example, is dysplastic. The dysplasia caused from sunburn, however, corrects itself as the sunburned skin heals.

Any source of irritation causing inflammation of an area will result in temporary dysplasia. Generally, when the source of irritation is removed the dysplasia will correct itself. Removing the irritant generally allows cell structure and organization to return to normal in a localized dysplasia.

Unfortunately, dysplasia can become permanent. This can occur when a source of irritation to a given area cannot be found and removed, or for completely unknown reasons. A continually worsening area of dysplasia can develop into an area of malignancy (**cancer**). Tendencies toward dysplasia can be genetic. They may also result from exposure to irritants or toxins, such as cigarette smoke, viruses, or chemicals.

CERVICAL DYSPLASIA The Pap smear, a medical procedure commonly performed on women, is a test for dysplasia of a woman's cervix. The cervix is the opening to a woman's uterus that extends into the vagina. It is a common area where cancers may develop. A Pap smear involves sampling the outer cells of a woman's cervix to look for microscopic cellular changes indicative of dysplasia, or abnormal tissue changes. Less than five percent of Pap smears indicate cervical dysplasia. Cervical dysplasia is most common in women who are 25 to 35 years old.

The degree of dysplasia present in cervical cells can be used as an indicator for progression to a cancerous condition. Early treatment of cervical dysplasia is very effective in halting progression of the dysplasia to cancer. Essentially, all sexual risk factors correlate with dysplasia. Exposure to the AIDS virus (HIV) or certain strains of human papilloma virus (HPV) raises a woman's risk to develop cervical dysplasia. Increased risk is also linked to having unprotected sex at an early age, having unprotected sex with many partners, or becoming pregnant before age 20. Smoking increases a woman's risk to develop cervical dysplasia. Prenatal exposure to diethylstilbestrol (DES), a hormonal drug prescribed from 1940 to 1971 to reduce miscarriages, also increases a woman's risk for cervical dysplasia. Exactly how these risk factors are connected to cervical dysplasia is not well understood.



Dysplasia is characterized by abnormal cell organization in body tissues. The tissue sample above shows a variety of cell shapes and arrangements typical of this disorder. *(Photo Researchers, Inc.)*

The American Cancer Society recommends that all women begin yearly Pap tests at age 18, or when they become sexually active, whichever occurs earlier. If a woman has had three negative annual Pap tests in a row, this test may be done less often at the judgment of a woman's health care provider.

Generalized dysplasia

A generalized dysplasia often presents as multiple malformations in a variety of structures. Any structural consequences are due to the particular tissue organization defect and the spectrum of organs that utilize the dysplastic tissue. Generalized dysplasias are often genetic. They may be inherited or occur due to a new genetic change in an individual. The structural problems associated with generalized dysplasias usually begin during embryonic development.

This type of dysplasia is classified according to the specific tissue affected. Generalized dysplasias account

KEY TERMS

Acondroplasia—An autosomal dominant form of dwarfism caused by a defect in the formation of cartilage at the ends of long bones. Affected individuals typically have short limbs, a large head with a prominent forehead and flattened profile, and a normal-sized trunk.

Amastia—A birth defect involving absent breast(s).

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Cartilage—Supportive connective tissue which cushions bone at the joints or which connects muscle to bone.

Chondrocyte—A specialized type of cell that secretes the material which surrounds the cells in cartilage.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Clubfoot—Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

***de novo* mutation**—Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DNA mutation analysis—A direct approach to the detection of a specific genetic mutation or mutations using one or more laboratory techniques.

Dysplasia—The abnormal growth or development of a tissue or organ.

Ectoderm—The outermost of the three embryonic cell layers, which later gives rise to the skin, hair, teeth, and nails.

Ectrodactyly—A birth defect involving a split or cleft appearance of the hands and/or feet, also referred to as a "lobster-claw malformation."

Epiphyses—the growth area at the end of a bone.

(continued)

for some important groups of inherited disorders including the skeletal dysplasias and ectodermal dysplasias.

SKELETAL DYSPLASIAS Skeletal dysplasias affect the growth, organization, and development of the bony skeleton. These conditions are always genetic. The effects of skeletal dysplasias vary. A mild skeletal dysplasia may cause someone to be of shortened height without any other complication. Other skeletal dysplasias may severely reduce height, causing dwarfism with disproportion and other bone deformity. The most severe skeletal dysplasias are incompatible with life, causing babies to die before or soon after birth.

The skeletal dysplasias include **achondroplasia**, **hypochondroplasia**, **thanatophoric dysplasia**, **achondrogenesis**, **diastrophic dysplasia**, atelosteogenesis, **spondyloepiphyseal dysplasia**, Kniest dysplasia, **Stickler syndrome**, pseudoachondoplasia, **metaphyseal dysplasia**, and several others.

KEY TERMS (CONTINUED)

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term embryo is used prior to the third month.

Fibroblast—Cells that form connective tissue fibers like skin.

Founder effect—Increased frequency of a gene mutation in a population that was founded by a small ancestral group of people, at least one of whom was a carrier of the gene mutation.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genitals—The internal and external reproductive organs in males and females.

Gonads—The organ that will become either a testis (male reproductive organ) or ovary (female reproductive organ) during fetal development.

Hallucal polydactyly—The appearance of an extra great toe.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Hypertelorism—A wider-than-normal space between the eyes.

Hyperthermia—Body temperature that is much higher than normal (i.e. higher than 98.6°F).

Hypochondroplasia—An autosomal dominant form of dwarfism whose physical features are similar to those of achondroplasia but milder. Affected individuals have mild short stature and a normal facial appearance.

Linkage analysis—A method of finding mutations based on their proximity to previously identified genetic landmarks.

Metacarpal—A hand bone extending from the wrist to a finger or thumb.

Metaphyses—The growth zone of the long bones located between the epiphyses the ends (epiphyses) and the shaft (diaphysis) of the bone.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nanism—Short stature.

Ovary—The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

Philtrum—The center part of the face between the nose and lips that is usually depressed.

Sulfate—A chemical compound containing sulfur and oxygen.

Testes—The male reproductive organs that produce male reproductive cells (sperm) and male hormones.

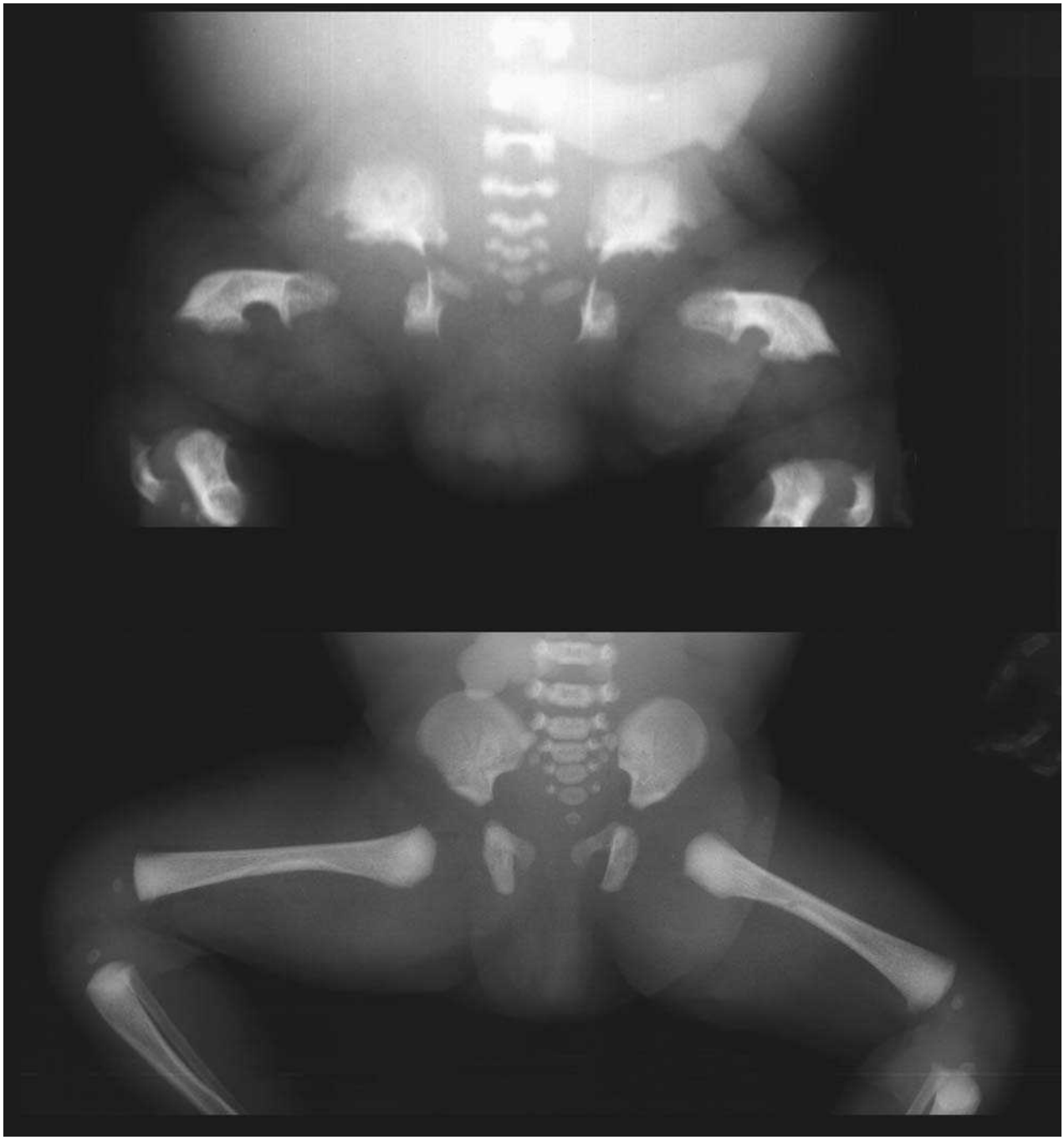
Tetralogy of Fallot—A congenital heart defect consisting of four (tetralogy) associated abnormalities: ventricular septal defect (VSD—hole in the wall separating the right and left ventricles); pulmonic stenosis (obstructed blood flow to the lungs); the aorta "overrides" the ventricular septal defect; and thickening (hypertrophy) of the right ventricle.

Tissue—Group of similar cells that work together to perform a particular function. The four basic types of tissue include muscle, nerve, epithelial, and connective tissues.

Vertebra—One of the 23 bones which comprise the spine. *Vertebrae* is the plural form.

Achondroplasia is a common, highly recognizable skeletal dysplasia. This disorder occurs in approximately one in 20,000 live births. Achondroplasia affects bone growth resulting in short stature, a large head, characteristic facial features, and disproportionately short arms and legs. This disorder is caused by a mutation in a single **gene** called fibroblast growth factor receptor three (FGFR3). Achondroplasia may be inherited like most generalized dysplasias, but more commonly it occurs due to a new mutation in a family. Over 80% of cases of achondroplasia are sporadic, or due to new mutations. The appearance of new mutations for achondroplasia is more frequently observed in children born to older fathers.

Hypochondroplasia is a common, milder skeletal dysplasia caused by different mutations in the gene responsible for achondroplasia, the FGFR3 gene. People with hypochondroplasia display varying degrees of short



Infants with thanatophoric dysplasia have abnormal pelvic and leg bone formation. The affected infant shown on top has the characteristic "telephone receiver" shape. An infant with normal bone formation is shown on the bottom for comparison. *(Greenwood Genetic Center)*

stature and disproportion of limbs. People with mild symptoms may never be diagnosed. The body of a person with hypochondroplasia appears short and broad with a long torso and short limbs. Lifespan is normal. Like achondroplasia, hypochondroplasia is inherited in an autosomal dominant manner.

ECTODERMAL DYSPLASIAS Ectodermal dysplasias affect the growth and development of tissues derived from the early outer layer of embryonic tissue known as the ectoderm. Tissues derived from the ectoderm include hair, fingernails, skin, sweat glands, and teeth. People with ectodermal dysplasias display abnormalities in at

least two derivatives of the ectoderm. **Ectodermal dysplasia** (ED) can take many different forms because so many tissues are derived from the ectoderm. Over 150 types of ectodermal dysplasias have been identified.

The effects of ectodermal dysplasias range from mild to severe. They are divided into two major groups based on the presence or absence or normal sweating. Sweat production is normal in hidrotic (sweating) types and reduced in hypohidrotic (decreased sweating) types. Types with reduced or absent sweating are generally more severe.

Christ-Siemens-Touraine syndrome (CST), a hypohidrotic (decreased sweating) ectodermal dysplasia, is a common, well-understood type of ectodermal dysplasia. People with this type of ectodermal dysplasia are not able to sweat or form tears normally. They are very sensitive to light and are not able to control their body temperature well due to their reduced sweating. Intelligence is normal. People with CST often have small or missing teeth, eyebrows, and eyelashes. Head hair is usually sparse, but fingernails are normal. CST is usually X-linked recessive, affecting only males with full symptoms of the disease. In some cases, female carriers show mild symptoms of the disease. Rarer autosomal dominant and autosomal recessive forms can affect males and females.

Clouston ectodermal dysplasia, a hidriotic (sweating) ectodermal dysplasia, also known as ectodermal dysplasia 2 (ED2) is found more commonly in people of French Canadian descent. People with this form of ED have partial to total baldness with normal teeth, severely abnormal fingernails, and darkly pigmented areas of skin, especially over joints. They have underdeveloped eyebrows and eyelashes and may be born with teeth. They may also have thickened skin on the soles of their feet and the palms of their hands. Features including mental retardation and strabismus, or crossed eyes, may occur with this disorder, however intelligence is usually normal. This form of ED is inherited in an autosomal dominant manner. Any affected person has a 50% chance to pass the disorder to each of their children.

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Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

FACES: The National Craniofacial Assocation. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

Greenberg Center for Skeletal Dysplasias. 600 North Wolfe St., Blalock 1012C, Baltimore, MD 21287-4922. (410) 614-0977 <http://www.med.jhu.edu/Greenberg.Center/Greenbrg.htm>.

Johns Hopkins University-McKusick Nathans Institute of Genetic Medicine 600 North Wolfe St., Blalock 1008, Baltimore, MD 21287-4922. (410) 955-3071.

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408. (806) 737-8186 or (888) LPA-2001. lpadatabase@juno.com. <http://www.lpaonline.org>.

National Foundation for Ectodermal Dysplasias. PO Box 114, 410 E Main, Mascoutah, IL 62258-0114. (618) 566-2020. Fax: (618) 566-4718. <http://www.nfed.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Judy C. Hawkins, MS

Dysplasia giantism syndrome X-linked (DGSX) *see* **Simpson-Golabi-Behmel syndrome**

Dystonia

Definition

Dystonia is a group of complex neurological movement disorders. While the disorders vary in their symptoms, causes, progression, and treatment, dystonia is characterized by involuntary muscle contractions and spasms that result in abnormal postures and movements. Focal dystonias—which affect a single part of the body, such as the face, arms, or vocal chords—are the most common.

Description

Dystonia is not a single disease, but a group of disorders with a variety of symptoms. The most common characteristic of dystonia is twisting, repetitive, and sometimes painful movements that affect a specific part of the body, such as the arms, legs, trunk, neck, eyelids,

KEY TERMS

Basal ganglia—A section of the brain responsible for smooth muscular movement.

Blepharospasm—A focal dystonia marked by excessive blinking and involuntary closing of the eyes.

Cervical dystonia—A focal dystonia that causes neck muscles to contract involuntarily–leading to abnormal movements and posture of the head and neck. Also known as spasmodic torticollis.

Early on-set dystonia—Dystonia that begins in adolescence. Most common among Jewish persons of Eastern European ancestry.

Limb dystonia—Involuntary cramp or spasm that affects the hands. Also known as writer's cramp.

Primary dystonia—Dystonia that has no connection to disease or injury. Often hereditary.

Secondary dystonia—Dystonia that occurs due to disease, injury, or another non-hereditary factor. Also known as symptomatic dystonia.

Spasmodic dysphonia—A focal dystonia that causes involuntary "spasms" of the vocal cords—leading to interruptions of speech and a decrease in voice quality.

face, or vocal cords. Cervical dystonia, which affects the head and neck, is the most common adult form of dystonia, followed by blepharospasm (eyelids), spasmodic dysphonia (larynx), and limb dystonias (hands).

Researchers believe that dystonia is caused by a malfunction in the basal ganglia, the part of the brain involved in regulating voluntary and involuntary movement. A Berlin neurologist, Hermann Oppenheim, first coined the term "dystonia" in 1911 after observing muscle spasm and variation in muscle tone in several of his young patients. The term was widely accepted and used by neurologists; however, the definition has changed over time.

Today dystonia is classified in several ways, based on cause, location, and age at onset.

Dystonia can be caused by many different factors. It may occur due to trauma, stroke, certain infections and diseases (e.g. **Wilson disease**, multiple sclerosis), reactions to certain neuroleptic or antipsychotic drugs (e.g. haloperidol or chlorpromazine), birth injury, or heavy-metal or carbon monoxide poisoning. This type of dystonia is called secondary or symptomatic dystonia. About half of dystonia cases have no connection to disease or injury and are referred to as primary dystonia. Many of these cases appear to be inherited.

The most useful classification for physicians is location, or distribution of the dystonia. Focal dystonia involves a single body part while multifocal dystonia affects multiple body parts. In generalized dystonia, symptoms begin in an arm or a leg and advance, eventually affecting the rest of the body.

The patient's age at the onset of symptoms helps physicians identify the cause and determine the probability of disease progression. Dystonia that begins in childhood is often hereditary, begins in the leg or (less commonly) the arm, and may progress to other parts of the body. Dystonia that begins in adolescence (early on-set dystonia) may be hereditary, often begins in the arm or neck, and is more likely to progress than the childhood form. Adult-onset dystonia typically begins as focal or multifocal and is sporadic in origin.

Genetic profile

The majority of primary dystonia cases are believed to be hereditary and occur as the result of a faulty **gene**. Most cases of early-onset primary dystonia are due to a mutation in the DYT-1 gene, which was first identified as a factor in the disorder in 1987.

Dystonia appears when an individual has one copy of the mutated gene and one copy of the normal gene; however, only 30–40% of individuals with the mutated genes develop symptoms.

Demographics

Dystonia affects more than 300,000 people in North America, affecting all races and ethnic groups. Early onset idiopathic torsion dystonia has a higher frequency among Ashkenazi Jews—Jews of Eastern European ancestry.

Dystonia is the third most common movement disorder, after **Parkinson disease** and tremor.

Signs and symptoms

Early symptoms of dystonia may include a deterioration in handwriting, foot cramps, tremor, voice or speech difficulties, and a tendency of one foot to pull up or drag while walking. Initially, the symptoms may be very mild and only noticeable after prolonged exertion, stress, or fatigue. Over a period of time, the symptoms may become more noticeable and widespread.

Symptoms may first occur in childhood (between the ages of 5 and 17 years) or early adulthood. In general, the

earlier the onset of symptoms, the greater the chance that the disease will progress with advancing age.

Diagnosis

There is no specific diagnostic test for dystonia and the diagnosis is often based on clinical signs and symptoms. Diagnosis may be difficult because the signs are similar to those of other disorders; the involuntary muscle contractions are often incorrectly attributed to stress, stiff neck, dry eyes, tics, or psychogenic or neurological disorders. According to Mount Sinai Medical Center, 90% of dystonia patients are initially misdiagnosed.

One thing that is helpful in differentiating dystonic movements from those caused by other disorders is the timing of the movements. Dystonic movements tend to increase during activity, nervousness, and emotional stress; and usually disappear during sleep.

Treatment and management

There is no cure for dystonia. However, symptoms such as spasms and pain can usually be managed with a combination of treatments.

No one treatment has proven universally effective. A physician's approach to treatment is typically three-tiered, encompassing oral medications, injections of therapeutic agents (e.g. botulinum toxin) directly into dystonic muscle, and surgery. Surgery, which involves cutting nerves and muscles or placing a lesion in the basal ganglia to reduce movement, is usually reserved for the most severe cases. Alternative medicine, such as physical therapy, speech therapy, and biofeedback, may also have a role in treatment management.

The cause and location of a patient's dystonia will play a factor in the treatment methods chosen by the physician. In secondary dystonia, treating the underlying cause may prove effective in improving or eliminating the associated symptoms. Patients with focal dystonia often respond best to targeted methods—such as injections of botulinum toxin or surgery—while patients with dystonia may first need to be treated with oral medications to alleviate the multiple symptoms.

Prognosis

Dystonia is not fatal; however, it is a chronic disorder and prognosis can be difficult to predict.

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Bachmann-Strauss Dystonia & Parkinson Foundation, Inc. Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1490, New York, NY 10029. (212) 241-5614. <http://www.dystonia-parkinsons.org>.

Dystonia Medical Research Foundation. One East Wacker Dr., Suite 2430, Chicago, IL 60601. (312) 755-0198. <http://www.dystonia-foundation.org>.

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Michelle L. Brandt

Dystrophia myotonica 2 *see* **Myotonic dystrophy**

E

Ectodermal dysplasia

Definition

The ectodermal dysplasias are a group of hereditary conditions characterized by abnormal hair, teeth, fingernails and toenails, and sweat glands.

Description

All ectodermal dysplasias have a genetic etiology and involve abnormal development and growth of ectodermally derived tissues. The ectoderm is the outermost layer of the developing embryo, which gives rise to the hair, teeth, nails, and skin. More than 100 different ectodermal dysplasia conditions have been described in the medical literature. The most common of these is hypohidrotic ectodermal dysplasia, which may account for up to 80% of all ectodermal dysplasias.

Other ectodermal dysplasia conditions include ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome, hidrotic ectodermal dysplasia (Clouston syndrome), Hay-Wells syndrome, incontintentia pigmenti, Rapp-Hodgkin syndrome, tricho-dento-osseous syndrome, and tooth-nail (Witkop) syndrome. Each of these conditions appears to account for 1–4% of all ectodermal dysplasias.

Most ectodermal dysplasia conditions are associated with sparse hair that has abnormal texture. The hair may appear thin, dry, and brittle. In some cases, premature balding may occur.

The teeth of those with ectodermal dysplasia are typically abnormal and reduced in number. A characteristic conical and sharply pointed tooth shape is often present. In some cases, the majority of teeth are missing.

In some ectodermal dysplasia conditions, the fingernails and toenails may be absent or abnormally formed. The nails may be thickened, thinned, brittle, or display unusual ridging or pitting.

The skin may be thin, show abnormal pigmentation, and be prone to eczema (a condition of dry skin characterized by inflammation and itching). The nasal and respiratory passages may be dry, leading to abnormal discharges and increased infections. In hypohydrotic ectodermal dysplasia, the sweat glands are reduced in number, which may lead to dangerous hyperthermia (high body temperature).

Other abnormalities that may occur in the ectodermal dysplasia conditions include amastia (absent mammary glands), cleft lip and/or palate, ectrodactyly (split hand or split foot), and abnormal bands of skin in the mouth or connecting the eyelids.

Many individuals with ectodermal dysplasia have normal cognitive function. A minority of cases may involve some degree of mental retardation. In the case of hypohydrotic ectodermal dysplasia, untreated hyperthermic episodes can lead to brain damage and cognitive impairment.

Genetic profile

Hypohydrotic ectodermal dysplasia is inherited in an X-linked recessive manner. Sixty to 75% of carrier females may show variable manifestations of the condition. The responsible **gene** has been named EDA; it has been mapped to the Xq12-q13.1 chromosomal region but has not yet been identified.

Incontinentia pigmenti is caused by chromosomal rearrangements disrupting the Xp11 region (type I incontintentia pigmenti) or by a **gene mapping** to Xq28 (type II or familial incontintentia pigmenti). Both forms appear to be lethal in males, as nearly all affected patients (97–98%) are female.

Most other ectodermal dysplasias are transmitted in an autosomal dominant fashion. Rarely, autosomal recessive transmission may occur.

The molecular genetics of the ectodermal dysplasia conditions are poorly understood. Investigation has been hampered by the great variability displayed by many of these conditions, similar features shown by different ectodermal dysplasias, and genetic heterogeneity (differ-

KEY TERMS

Amastia—A birth defect involving absent breast(s).

Dysplasia—The abnormal growth or development of a tissue or organ.

Ectoderm—The outermost of the three embryonic cell layers, which later gives rise to the skin, hair, teeth, and nails.

Ectrodactyly—A birth defect involving a split or cleft appearance of the hands and/or feet, also referred to as a "lobster-claw malformation."

Hyperthermia—Body temperature that is much higher than normal (i.e. higher than 98.6°F).

ent genetic alterations producing identical physical features). As with many other human genetic conditions, mouse models are being used to identify candidate genes that may be responsible for these disorders.

Demographics

The exact incidence of ectodermal dysplasia conditions has not yet been studied accurately and is not known. One published report estimated the incidence of these conditions collectively as 7 per 10,000 births. The disorders have been reported in individuals and families of diverse ethnic backgrounds. One early description of an ectodermal dysplasia came from Charles Darwin, who cited a report of an affected individual from the Indian subcontinent in an 1897 publication.

Signs and symptoms

Most ectodermal dysplasia conditions cause significant dental abnormalities. In some cases, the majority of the primary ("baby") and secondary ("adult") teeth are missing. Teeth that are present may show a characteristic conical, pointed shape ("peg-teeth"), or have abnormal enamel that is prone to cavities.

Hair is often thin with an abnormal texture. In hypohydrotic ectodermal dysplasia, the scalp hair is thin during childhood and ultimately shows premature balding. Although body hair, eyebrows, and eyelashes are also sparse in this condition, beard and mustache hair are normal. Hair is also sparse in EEC syndrome. In trichodento-osseous syndrome and Hay-Wells syndrome, the hair is sparse, coarse, and wiry. Individuals with incontinentia pigmenti may have patchy, bald areas of abnormal skin on the scalp. Frequent scalp infections occur in many of the ectodermal dysplasias.

A variety of skin abnormalities may occur in ectodermal dysplasia conditions. The skin may be dry, thin, and prone to eczema, infection, cracking, bleeding, and other problems. In hypohydrotic ectodermal dysplasia, sebaceous glands (the oil glands within the skin) are absent, causing severe dryness. Increased pigmentation may occur around the eyes (in hypohydrotic dysplasia), over the joints (in hidrotic ectodermal dysplasia), or in a linear pattern over the trunk (in incontinentia pigmenti). Hyperkeratosis, or thickened skin, occurs on the palms and soles of the feet in hidrotic ectodermal dysplasia. Reddening and blistering of the skin may occur during infancy in incontintentia pigmenti. In Hay-Wells syndrome, abnormal bands of skin may occur between the upper and lower jaws and between the eyelids.

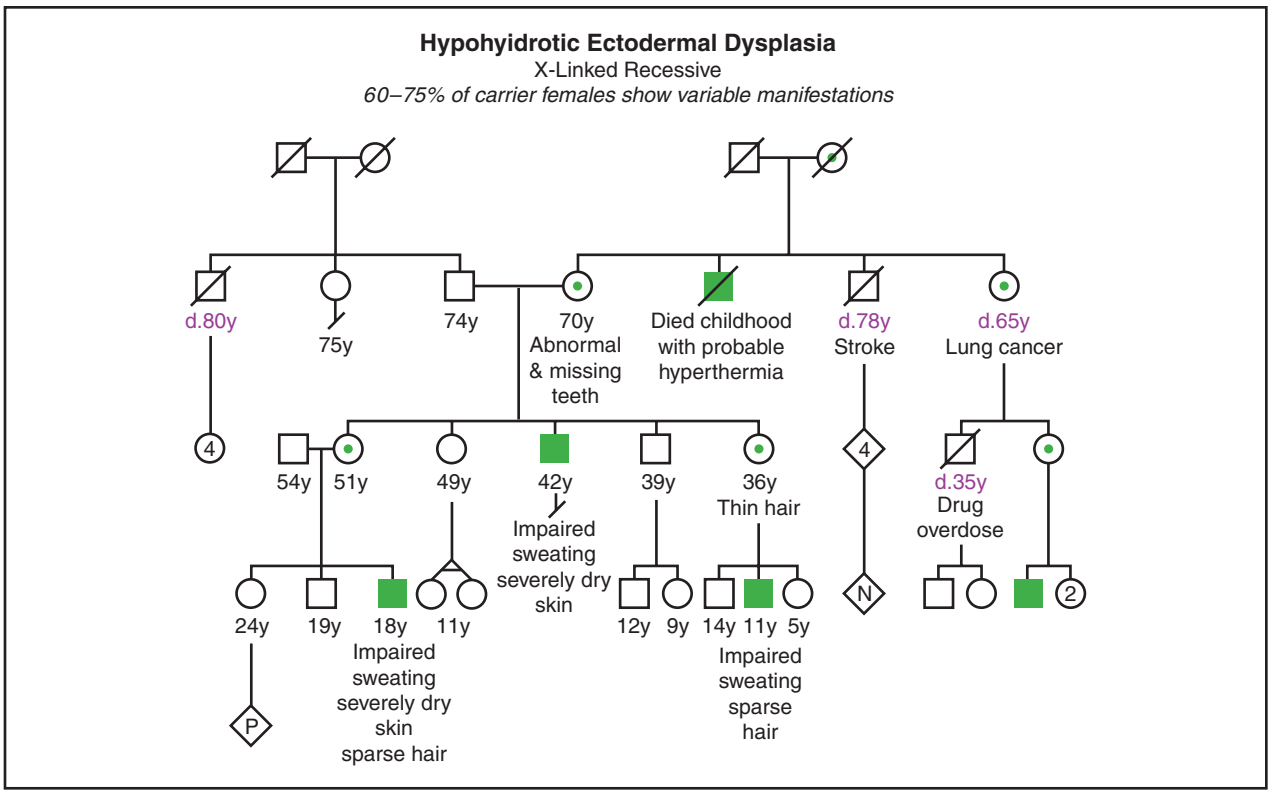
Decreased numbers of sweat glands and associated impaired sweating ability is an important feature of hypodrotic ectodermal dysplasia. This can lead to life-threatening hyperthermia in hot environments or with physical exertion. Sweating is normal in most other ectodermal dysplasias.

Many ectodermal dysplasias involve abnormalities of the mucous membranes. Production of tears and saliva may be deficient. In hypohydrotic ectodermal dysplasia, the mucous glands in the respiratory tract may be absent or decreased in number, leading to dryness, infections, and an unusual foul-smelling secretion known as ozena. In some cases, dryness of the pharynx and larynx may affect the quality of the voice.

Finger and toenails are abnormal in many of the ectodermal dysplasias. In EEC syndrome, the nails may be thin and brittle. Nails may be absent or abnormally formed in Hay-Wells syndrome, Rapp-Hodgkin syndrome, hidrotic ectodermal dysplasia, tooth and nail syndrome, and incontintentia pigmenti. Nails are normal in hypohydrotic ectodermal dysplasia.

Some individuals with ectodermal dysplasia, particularly those with EEC syndrome, may have hearing impairment.

Structural birth defects may occur in some ectodermal dysplasias. In EEC, Hay-Wells, and Rapp-Hodgkin syndromes, **cleft lip and palate** may occur. EEC is also characterized by split hand/split foot (or "lobster claw") malformations and genitourinary anomalies. Amastia (absence of the breast) may occur in hypohydrotic ectodermal dysplasia and breasts may be underdeveloped in incontintia pigmenti and EEC syndrome. Some individuals with incontinentia pigmenti may have defects of the eye (such as congenitally crossed eyes, cataracts, or atrophy of the optic nerve) or central nervous system (such as a small head size, mental retardation, or seizures).



(Gale Group)

Diagnosis

The diagnosis of an ectodermal dysplasia condition is typically based on clinical findings (physical examination, medical and family history). With the exception of type I incontinentia pigmenti, there are no laboratory studies that are considered diagnostic. High resolution chromosome study may be considered diagnostic for type I incontintentia pigmenti as it can reveal the X chromosome rearrangements that appear to cause the condition.

The high degree of variability within and overlap between the different ectodermal dysplasia conditions can lead to difficulty identifying the specific syndrome. The presence or absence of nail and sweat gland involvement are important distinguishing features.

In hypohydrotic ectodermal dysplasia, determining whether or not a female relative of an affected male also carries the EDA gene may be difficult. A variety of clinical tests based on sweat pore and dental analysis have been attempted, but are considered unreliable. Linkage analysis by way of tracing the Xq12-13 gene locus through the family is considered to be the best way of determining carrier status. When linkage analysis is successful, it may also be used for prenatal diagnosis.

Treatment and management

In hypohydrotic ectodermal dysplasia, males are at risk for hyperthermia and potential central nervous system damage or death. Hot environments and fevers must be avoided or managed with cooling methods, such as misting the skin with water. Air conditioning of home, school, and work environments is considered essential. The dry nasal passages may be treated with moisturizing inhalers or other solutions. Various skin treatments may be used to prevent cracking, bleeding, and infection.

Early and extensive dental work is required in most ectodermal dysplasia conditions. In childhood, successive dentures may be used, while dental implants and bridges may be used in adults. Orthodontic treatment may also be necessary.

The abnormal hair in the ectodermal dysplasias is primarily a cosmetic problem and may be managed with wigs.

In EEC, Rapp-Hodgkin syndrome, and Hay-Wells syndrome, clefting of the lip and palate requires surgical correction, with treatment of any associated speech, dental, or hearing problems.

Hand and foot malformations in EEC may require orthopedic or plastic surgery, and/or occupational ther-

apy. The abnormal skin banding that may occur in the mouth and between the eyelids in Hay-Wells syndrome also requires surgical correction.

Prognosis

Among males with hypohydrotic ectodermal dysplasia, unrecognized episodes of hyperthermia are a dangerous complication. The mortality rate during infancy and early childhood in affected, undiagnosed males is 20% due to neurologic damage associated with hyperthermic episodes. If affected males are diagnosed and managed appropriately, a normal life expectancy and normal intelligence can be expected.

Otherwise, the tissue abnormalities and birth defects that occur in the ectodermal dysplasias are usually not life-threatening.

These conditions typically do not cause mental retardation, although a minority of cases of incontintenti pigmenti and EEC syndrome may involve cognitive impairment.

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Jennifer Roggenbuck, MS, CGC

Edwards syndrome *see* **Trisomy 18**

Ehlers-Danlos syndrome

Definition

The Ehlers-Danlos syndromes (EDS) refer to a group of inherited disorders that affect collagen structure and function. Genetic abnormalities in the manufacturing of collagen within the body affect connective tissues, causing them to be abnormally weak.

Description

Collagen is a strong, fibrous protein that lends strength and elasticity to connective tissues such as the skin, tendons, organ walls, cartilage, and blood vessels. Each of these connective tissues requires collagen tailored to meet its specific purposes. The many roles of collagen are reflected in the number of genes dedicated to its production. There are at least 28 genes in humans that encode at least 19 different types of collagen. Abnormalaties in these genes can affect basic construction as well as the fine-tuned processing of the collagen.

Genetic profile

There are numerous types of EDS, all caused by changes in one of several genes. The manner in which EDS is inherited depends on the specific **gene** involved. There are three patterns of **inheritance** for EDS: autosomal dominant, autosomal recessive, and X-linked (extremely rare).

Chromosomes are made up of hundreds of small units known as genes, which contain the genetic material necessary for an individual to develop and function. Humans have 46 chromosomes, which are matched into 23 pairs. Because chromosomes are inherited in pairs, each individual receives two copies of each chromosome and likewise two copies of each gene.

Changes or mutations in genes can cause genetic diseases in several different ways, many of which are represented within the spectrum of EDS. In autosomal dominant EDS, only one copy of a specific gene must be changed for a person to have EDS. In autosomal recessive EDS, both copies of a specific gene must be changed for a person to have EDS. If only one copy of an autosomal recessive EDS gene is changed, the person is referred to as a carrier, meaning they do not have any of the signs or symptoms of the disease itself, but carry the possibility of passing on the changed gene to a future child. In X-linked EDS, a specific gene on the X chromosome must be changed. This affects males and females differently because males have one and females have two X chromosomes.

As of 2001 the few X-linked forms of EDS fall under the category of X-linked recessive. As with autosomal recessive, this implies that both copies of a specific gene must be changed for a person to be affected. However, because males only have one X chromosome, they are affected if an X-linked recessive EDS gene is changed on their single X chromosome. That is, they are affected even though they have only one changed copy. On the other hand, that same gene must be changed on both of the X chromosomes in a female for her to be affected.

Although there is much information regarding the changes in genes that cause EDS and their various inheritance patterns, the exact **gene mutation** for all types of EDS is not known.

Demographics

EDS was originally described by Dr. Van Meekeren in 1682. Dr. Ehlers and Dr. Danlos further characterized the disease in 1901 and 1908, respectively. Today, according to the Ehlers-Danlos National Foundation, one in 5,000 to one in 10,000 people are affected by some form of EDS.

Signs and symptoms

EDS is a group of **genetic disorders** that usually affects the skin, ligaments, joints, and blood vessels. Classification of EDS types was revised in 1997. The new classification involves categorizing the different forms of EDS into six major subtypes including classical, hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis, and a collection of rare or poorly defined varieties. This new classification is simpler and based on descriptions of the actual symptoms.

Classical type

Under the old classification system, EDS classical type was divided into two separate types: type I and type II. The major symptoms involved in EDS classical type affect the skin and joints. The skin has a smooth, velvety texture and bruises easily. Affected individuals typically have extensive scarring, particularly at the knees, elbows, forehead, and chin. The joints are hyperextensible, so there is a tendency towards dislocation of the hip, shoulder, elbow, knee, or clavicle. Due to decreased muscle tone, affected infants may experience a delay in reaching motor milestones. Children may have a tendency to develop hernias or other organ shifts within the abdomen. Sprains and partial or complete joint dislocations are also common. Symptoms can range from mild to severe. EDS classical type is inherited in an autosomal dominant manner.

There are three major clinical diagnostic criteria for EDS classical type. These include skin hyperextensibility, unusually wide scars, and joint hypermobility. At this time there is no definitive test for the diagnosis of classical EDS. Both **DNA** and biochemical studies have been used to help identify affected individuals. In some cases, a skin biopsy has been found to be useful in confirming a diagnosis. Unfortunately, these tests are not sensitive enough to identify all individuals with classical EDS. If there are multiple affected individuals in a family, it may be possible to perform prenatal diagnosis using a DNA information technique known as a linkage study.

Hypermobility type

Excessively loose joints are the hallmark of this EDS type, formerly known as EDS type III. Both large joints,

KEY TERMS

Arthrochalasia—Excessive loosness of the joints.

Blood vessels—General term for arteries, veins, and capillaries, which transport blood throughout the body.

Cartilage—Supportive connective tissue that cushions bone at the joints or which connects muscle to bone.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Dermatosparaxis—Skin fragility caused by abnormal collagen.

Hernia—A rupture in the wall of a body cavity, through which an organ may protrude.

Homeopathic—A holistic and natural approach to health care.

Hyperextensibility—The ability to extend a joint beyond the normal range.

Hypermobility—Unusual flexibility of the joints, allowing them to be bent or moved beyond their normal range of motion.

Joint dislocation—The displacement of a bone.

Kyphoscoliosis—Abnormal front-to-back and side-to-side curvature of the spine.

Ligament—A type of connective tissue that connects bones or cartilage and provides support and strength to joints.

Osteoarthritis—A degenerative joint disease that causes pain and stiffness.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Tendon—A strong connective tissue that connects muscle to bone.

Uterus—A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

Vascular—Having to do with blood vessels.

such as the elbows and knees, and small joints, such as toes and fingers, are affected. Partial and total joint dislocations are common, and particularly involve the jaw, knee, and shoulder. Many individuals experience chronic limb and joint pain, although x rays of these joints appear normal. The skin may also bruise easily. **Osteoarthritis** is a common occurrence in adults. EDS hypermobility type is inherited in an autosomal dominant manner.

There are two major clinical diagnostic criteria for EDS hypermobility type. These include skin involvement (either hyperextensible skin or smooth and velvety skin) and generalized joint hypermobility. At this time there is no test for this form of EDS.

Vascular type

Formerly called EDS type IV, EDS vascular type is the most severe form. The connective tissue in the intestines, arteries, uterus, and other hollow organs may be unusually weak, leading to organ or blood vessel rupture. Such ruptures are most likely between ages 20 and 40, although they can occur any time, and may be life-threatening.

There is a classic facial appearance associated with EDS vascular type. Affected individuals tend to have large eyes, a thin pinched nose, thin lips, and a slim body. The skin is thin and translucent, with veins dramatically visible, particularly across the chest.

The large joints have normal stability, but small joints in the hands and feet are loose and hyperextensibile. The skin bruises easily. Other complications may include collapsed lungs, premature aging of the skin on the hands and feet, and ruptured arteries and veins. After surgery there may be poor wound healing, a complication that tends to be frequent and severe. Pregnancy also carries the risk complications. During and after pregnancy there is an increased risk of the uterus rupturing and of arterial bleeding. Due to the severe complications associated with EDS type IV, death usually occurs before the age of 50 years. A study of 419 individuals with EDS vascular type, completed in 2000, found that the median survival rate was 48 years, with a range of 6–73 years. EDS vascular type is inherited in an autosomal dominant manner.

There are four major clinical diagnostic criteria for EDS vascular type. These include thin translucent skin, arterial/intestinal/uterine fragility or rupture, extensive bruising, and characteristic facial appearance. EDS vascular type is caused by a change in the gene COL3A1, which codes for one of the collagen chains used to build Collage type III. Laboratory testing is available for this form of EDS. A skin biopsy may be used to demonstrate the structurally abnormal collagen. This type of biochemical test identifies more than 95% of individuals with EDS vascular type. Laboratory testing is recommended for individuals with two or more of the major criteria.

DNA analysis may also be used to identify the change within the COL3A1 gene. This information may be helpful for **genetic counseling** purposes. Prenatal testing is available for pregnancies in which an affected parent has been identified and the change in their DNA is known or their biochemical abnormality has been demonstrated.

Kyphoscoliosis type

The major symptom of kyphoscoliosis type, formerly called EDS type VI, is general joint looseness. At birth, muscle tone is poor, and motor skill development is subsequently delayed. Also, infants with this type of EDS have an abnormal curvature of the spine (**scoliosis**). The scoliosis becomes progressively worse with age, with affected individuals usually unable to walk by age 20 years. The eyes and skin are fragile and easily damaged, and blood vessel involvement is a possibility. The bones may also be affected as demonstrated by a decrease in bone mass. Kyphoscoliosis type is inherited in an autosomal recessive manner.

There are four major clinical diagnostic criteria for EDS kyphoscoliosis type. These include generally loose joints, low muscle tone at birth, scoliosis at birth (which worsens with age), and fragility of the eyes, which may give the white area of the eye a blue tint or cause the eye to rupture. This form of EDS is caused by a change in the PLOD gene on chromosome 1, which encodes the enzyme lysyl hydroxylase. A laboratory test is available in which urinary hydroxylysyl pryridinoline is measured. This urine test is extremely senstive and specific for EDS kyphoscolios type. Laboratory testing is recommended for infants with three or more of the major diagnostic criteria.

Prenatal testing is available if a pregnancy is known to be at risk and an identified affected family member has had positive laboratory testing. An **amniocentesis** may be performed in which fetal cells are removed from the amniotic fluid and enzyme activity is measured.

Arthrochalasia type

Dislocation of the hip joint typically accompanies arthrochalasia type EDS, formerly called EDS type VIIB. Other joints are also unusually loose, leading to recurrent partial and total dislocations. The skin has a high degree of stretchability and bruises easily. Individuals with this type of EDS may also experience mildly diminished bone mass, scoliosis, and poor muscle tone. Arthrochalasia type is inherited in an autosomal dominant manner.

There are two major clinical diagnostic criteria for EDS arthrochalasia type. These include severe generalized joint hypermobility and bilateral hip dislocation present at birth. This form of EDS is caused by a change in either of two components of Collage type I, called proa1(I) type A and proa2 (I) type B. A skin biopsy may be performed to demonstrate an abnormality in either component. Direct DNA testing is also available.

Dermatosparaxis type

Individuals with this type of EDS, once called type VIIC, have extremely fragile skin that bruises easily but does not scar excessively. The skin is soft and may sag, leading to an aged appearance even in young adults. Individuals may also experience hernias. Dermatosparaxis type is inherited in an autosomal recessive manner.

There are two major clinical diagnostic criteria for EDS dematosparaxis type. These include severe skin fragility and sagging or aged appearing skin. This form of EDS is caused by a change in the enzyme called procollagen I N-terminal peptidase. A skin biopsy may be preformed for a definitive diagnosis of dermatosparaxis type.

Other types

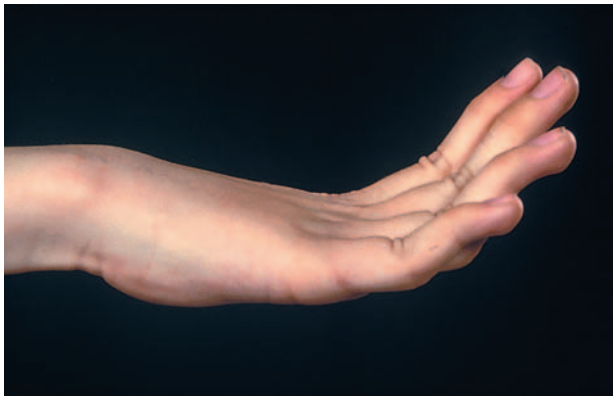
There are several other forms of EDS that have not been as clearly defined as the aforementioned types. Forms of EDS within this category may present with soft, mildly stretchable skin, shortened bones, chronic diarrhea, joint hypermobility and dislocation, bladder rupture, or poor wound healing. Inheritance patterns within this group include X-linked recessive, autosomal dominant, and autosomal recessive.

Diagnosis

Clinical symptoms such as extreme joint looseness and unusual skin qualities, along with family history, can lead to a diagnosis of EDS. Specific tests, such as skin biopsies, are available for diagnosis of certain types of EDS, including vascular, arthrochalasia, and dermatosparaxis types. A skin biopsy involves removing a small sample of skin and examining its microscopic structure. A urine test is available for the kyphoscoliosis type.

Management of all types of EDS may include genetic counseling to help affected individuals and their families understand the disorder and its impact on other family members and future children.

If a couple has had a child diagnosed with EDS, the chance that they will have another child with the same disorder depends on with what form of EDS the child has been diagnosed, and if either parent is affected by the same disease or not.



Hyperflexion of the joints, the ability to bend them beyond normal, is seen in most patients with Ehlers-Danlos syndrome. Overflexing of the hand is demonstrated by this patient. *(Custom Medical Stock Photo, Inc.)*

Individuals diagnosed with an autosomal dominant form of EDS have a 50% chance of passing the same disorder on to a child in each pregnancy. Individuals diagnosed with an autosomal recessive form of EDS have an extremely low risk of having a child with the same disorder.

X-linked recessive EDS is accompanied by a slightly more complicated pattern of inheritance. If a father with an X-linked recessive form of EDS passes a copy of his X chromosome to his children, his sons will be unaffected and his daughters will be carriers. If a mother is a carrier for an X-linked recessive form of EDS, she may have affected or unaffected sons, or carrier or unaffected daughters, depending on which X chromosome her child inherits from her and which sex chromosome is inherited from the father.

Prenatal diagnosis is available for specific forms of EDS, including kyphoscoliosis type and vascular type. However, prenatal testing is only a possibility in these types if the underlying abnormality has been found in another family member.

Treatment and management

Medical therapy relies on managing symptoms and trying to prevent further complications. There is no cure for EDS.

Braces may be prescribed to stabilize joints, although surgery is sometimes necessary to repair joint damage caused by repeated dislocations. Physical therapy teaches individuals how to strengthen muscles around joints and may help to prevent or limit damage.

Elective surgery is discouraged due to the high possibility of complications.

Alternative treatment

There are anecdotal reports that large daily doses (1–4 g) of vitamin C may help decrease bruising and aid in wound healing. Constitutional homeopathic treatment may be helpful in maintaining optimal health in persons with a diagnosis of EDS. Individuals with EDS should discuss these types of therapies with their doctor before beginning them on their own. Therapy that does not require medical consultation involves protecting the skin with sunscreen and avoiding activities that place stress on the joints.

Prognosis

The outlook for individuals with EDS depends on the type of EDS with which they have been diagnosed. Symptoms vary in severity, even within one subtype, and the frequency of complications changes on an individual basis. Some individuals have negligible symptoms while others are severely restricted in their daily life. Extreme joint instability and scoliosis may limit a person's mobility. Most individuals will have a normal lifespan. However, those with blood vessel involvement, particularly those with EDS vascular type, have an increased risk of fatal complications.

EDS is a lifelong condition. Affected individuals may face social obstacles related to their disease on a daily basis. Some people with EDS have reported living with fears of significant and painful skin ruptures, of becoming pregnant (especially those with EDS vascular type), of their condition worsening, of becoming unemployed due to physical and emotional burdens, and of social stigmatization in general.

Constant bruises, skin wounds, and trips to the hospital take their toll on both affected children and their parents. Prior to diagnosis, parents of children with EDS have found themselves under suspicion of child abuse.

Some people with EDS are not diagnosed until well into adulthood and, in the case of EDS vascular type, occasionally not until after death due to complications of the disorder. Not only may the diagnosis itself be devastating to the family, but in many cases other family members find out for the first time they are at risk for being affected.

Although individuals with EDS face significant challenges, it is important to remember that each person is unique with his or her own distinguished qualities and potential. Persons with EDS go on to have families, have careers, and become accomplished citizens, surmounting the challenges of their disease.

Resources

PERIODICALS

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"Ehlers-Danlos Syndromes: Revised Nosology, Villefranche, 1997." *American Journal of Medical Genetics* 77 (1998): 31–37.

"Living a Restricted Life with Ehlers-Danlos Syndrome." *International Journal of Nursing Studies* 37 (2000): 111–118.

ORGANIZATIONS

Elhers-Danlos National Foundation. 6399 Wilshire Blvd., Ste 203, Los Angeles, CA 90048. (323) 651-3038. Fax: (323) 651-1366. <http://www.ednf.org>.

Ehlers-Danlos Support Group—UK. PO Box 335, Farnham, Surrey, GU10 1XJ. UK. 01252 690 940. <http://www.atv.ndirect.co.uk>.

WEBSITES

GeneClinics. <http://www.geneclinics.org>.

Java O. Solis, MS

Elattoproteus syndrome *see* **Proteus syndrome**

Ellis-van Creveld syndrome

Definition

Ellis-van Creveld syndrome is an individually recognized genetic condition characterized by short stature and malformations of the heart, limbs, nails, and teeth. The name given to this condition originates from Richard W. B. Ellis of Scotland and Simon van Creveld of the Netherlands. Each had a patient with this syndrome in his care when the two met by chance in an English train car on the way to a pediatric conference in the late 1930s.

Description

Ellis-van Creveld (EvC) syndrome primarily affects the skeletal system, but is also associated with **congenital heart defects**. EvC syndrome is one of the six short rib polydactyly syndromes, or SRPS. There is considerable overlap between the features of these six syndromes. Clinical, radiological, and pathological studies are being conducted to determine if there are indeed six distinct SRPS, or if each is a different mutation at the **gene** that also causes Ellis-van Creveld syndrome.

Ellis-van Creveld syndrome is alternatively known as chondroectodermal **dysplasia** or mesoectodermal dysplasia. The name chondroectodermal dysplasia is meant to indicate a dysplasia, or abnormal growth or development, of the skeleton (chondro-) and the skin (ectodermal). The name mesoectodermal dysplasia is meant to indicate an abnormal growth or development of the skin (ectodermal) and primarily the middle portion of the bone (meso-). However, neither medically descriptive term defines the syndrome completely, and Ellis-van Creveld syndrome remains the most used name for both medical and common purposes.

Ellis-van Creveld syndrome is characterized by short arms and legs; short ribs; short fingers; polydactyly, or extra fingers or toes; and dysplastic, or abnormal, teeth and nails. Limb shortening is more noticeable in the legs than in the arms. Many older children affected by EvC syndrome develop knock-knee, or genu valgum, which may have to be corrected by orthopedic surgery. The underdeveloped ribs generally cause a condition known as pectus carinatum, in which the chest is narrow and elongated. A sixth finger on both hands occurs in all patients with EvC syndrome, while extra toes are observed in approximately 20% of the EvC syndrome population. Polydactyly in affected individuals is always symmetric. That is, if the left hand possesses a sixth finger, the right hand will also possess a sixth finger.

Dysplastic, or abnormal, teeth and nails are observed in all individuals with EvC syndrome. The most common dental anomalies are: teeth present at birth; wide spaces between permanent teeth; the late eruption of, or the complete lack of, some permanent teeth; and permanent teeth that more closely resemble baby teeth than permanent teeth. The most common nail abnormalities are absent or malformed fingernails or toenails. Thin, brittle hair is also observed in a majority of patients with EvC syndrome.

Congenital heart defects occur in approximately 50-60% of affected individuals. The most common cardiac abnormality observed is a common atrium rather than the normal two-chambered atrium. This "hole in the heart" can often be surgically repaired, resulting in normal heart function.

Genetic profile

Ellis-van Creveld syndrome is an autosomal, or non-sex linked, recessive condition. The gene responsible for EvC syndrome has been identified and its locus determined on the distal short arm of chromosome 4p. In 2000, it was shown that the EvC gene is the same gene that causes Weyers acrofacial dysostosis.

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Dysplasia—The abnormal growth or development of a tissue or organ.

Heterozygous—Having two different versions of the same gene.

Homozygous—Having two identical copies of a gene or chromosome.

Postaxial polydactyly—A condition in which an extra finger or toe is present outside of the normal fifth digit.

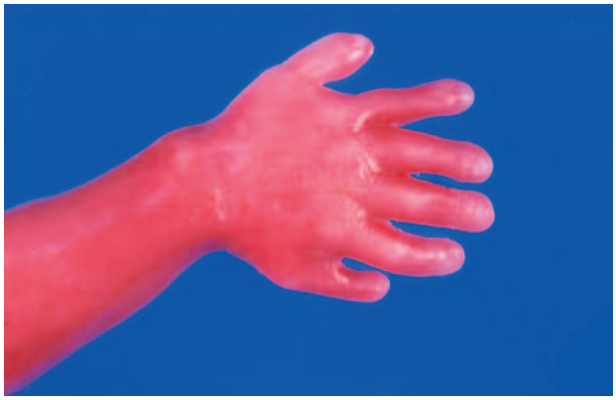
Primary atrial septation—An improper division of the atria of the heart, or a "hole in the heart," which results in the formation of a common atrium rather than the normal two-chambered atrium.

Short rib polydactyly syndromes—A collection of genetic disorders characterized by abnormally short ribs and extra fingers or toes. Research is ongoing to determine if these disorders are the result of mutations in a common gene.

Weyers acrofacial dysostosis—The condition resulting from a mutation of the same gene that shows mutation in Ellis-van Creveld syndrome. As is usually the case when comparing expressions of the same gene mutation, the single dose Weyers acrofacial dysostosis presents milder symptoms than the double dose Ellis-van Creveld syndrome.

Certain mutations in the EvC gene cause EvC syndrome. In order for EvC syndrome to appear, the affected child must inherit a mutation of this gene from each parent. The child must receive two abnormal genes.

When the child receives only a single copy of an abnormal gene that would cause EvC syndrome, that child is affected with Weyers acrofacial dysostosis. Weyers acrofacial dysostosis is an autosomal dominant condition characterized by tooth and nail abnormalities, extra fingers and toes, and milder limb anomalies than those observed in Ellis-van Creveld syndrome. As is often the case in homozygous disorders, EvC syndrome presents much more pronounced physically observable and potentially life-threatening signs than the corresponding heterozygous condition, Weyers acrofacial dysostosis.



Polydactyly, having extra fingers or toes, is a common feature in patients with Ellis van Creveld syndrome. *(Greenwood Genetic Center)*

Demographics

Ellis-van Creveld syndrome has an incidence of approximately one out of 150,000 live births. Ellis-van Creveld syndrome has a much higher occurrence among the Old Order Amish, an isolated and inbred religious community in Lancaster County, Pennsylvania.

As a homozygous condition, both parents of an affected child must carry the abnormal EvC gene. The parents of an affected child have a one in four chance of having additional children affected with EvC syndrome. The transmission of such homozygous **genetic disorders** is facilitated by the close association among potentially related individuals in a relatively small and isolated population such as that of the Amish. Also, a relatively high frequency of Ellis-van Creveld syndrome has been observed in the Aboriginal people of Western Australia. This high frequency has been attributed to a founder effect from Dutch castaways and genetic drift caused by the isolation and interbreeding of these peoples.

Signs and symptoms

Ellis-van Creveld syndrome is characterized by short limbs and short body length identifiable at birth. The average adult height range for those affected by EvC syndrome is 43–60 in (109–152 cm). The head and neck are generally unaffected other than possible abnormalities of the upper lip, and dental anomalies including delayed eruption of the permanent teeth, which are generally underdeveloped and more similar to a child's teeth than to those of an adult. EvC syndrome is further characterized by congenital heart defects, usually a single upper chamber (atrium) rather than the normal two upper chambers. Affected individuals have short, poorly developed ribs, which leads to a narrow chest; this is termed pectus carinatum.

Males affected by EvC syndrome may present abnormalities of the penis in which the urethral opening occurs on the underside of the penis rather than at the tip of the glans (hypospadias); they may also have one or both testicles undescended (cryptorchidism). Further skeletal anomalies associated with EvC syndrome include: low hips; a spur-like projection at the acetabula, the socket in the hipbone that accepts the head of the thighbone; a fusion of the capitate and hamate bones; two carpal bones, the fusion of which makes the formation of a fist difficult or impossible; knock-knee; clubfeet that turn down and in; and postaxial polydactyly, or extra fingers/toes that arise outside the normal fifth digit. Fingernails and toenails are generally malformed. Neurologically, mental retardation has been observed in patients with EvC syndrome, but it is not the norm. A brain abnormality of one of the normal cavities of the brain (Dandy-Walker syndrome) is also occasionally associated with EvC syndrome.

Diagnosis

Ultrasound imaging of developing fetuses can reveal the limb shortening and underdeveloped ribs that are characteristic of the short rib polydactyly syndromes (SRPS), which includes Ellis-van Creveld syndrome. An ultrasound scan is now available after the sixteenth week of gestation that may identify extra digits in the developing fetus.

Ellis-van Creveld syndrome is generally differentially diagnosed from the other SRPS by the additional presence of atrial abnormalities. However, it is often difficult to distinguish Ellis-van Creveld syndrome from two other forms of skeletal dysplasia. These are asphyxiating thoracic dysplasia (ATD), also known as Jeune syndrome; and short rib polydactyly syndrome (SRPS) type III, or Verma-Naumoff type SRPS. Individuals with Jeune syndrome often die of respiratory distress shortly after birth, whereas individuals diagnosed with EvC syndrome are more likely to die from congenital heart failure. Patients with Jeune syndrome often have extra fingers or toes; but, unlike those with EvC syndrome, this polydactyly is often not symmetric. Jeune syndrome does not present the nail and hair abnormalities seen in EvC syndrome. Older children can often be differentially diagnosed with Jeune syndrome rather than EvC syndrome if they develop kidney problems, which may also later lead to kidney failure as adults. Kidney dysfunction is not associated with Ellis-van Creveld syndrome.

Verma-Naumoff type SRPS is virtually indistinguishable from EvC syndrome prior to birth. However, individuals with Verma-Naumoff type SRPS also exhibit heart, kidney, and intestinal malformations that are not present in the Ellis-van Creveld population. Verma-Naumoff type SRPS has an essentially 100% mortality rate within hours of birth, as those affected die from respiratory distress. All three of these conditions arise from autosomal recessive **inheritance**. As of 2001, the genetic evidence is beginning to further the hypothesis that these three conditions are the result of mutations of the same gene on chromosome 4p that has been identified as the cause of Ellis-van Creveld syndrome.

Treatment and management

Genetic counseling of individuals affected with either Ellis-van Creveld syndrome or the allelic disorder, Weyers acrofacial dysostosis, may prevent the conception of children with EvC syndrome. Congenital heart defects associated with Ellis-van Creveld syndrome may be surgically corrected. The potential outcome of such a procedure is normal heart function. Extra fingers or toes (polydactyly) can be surgically removed shortly after birth. This is more a cosmetic treatment than a necessary one in the case of fully developed extra digits. If a person affected with EvC syndrome develops genu valgum (knock-knee), he or she may require orthopedic surgery to straighten the legs at the knee. Dental treatment also has an important role in management of Ellis-van Creveld syndrome.

Many people of extremely short stature adapt their surroundings to their size. Others choose to undergo one of the bone lengthening procedures that have increasingly become available. These bone lengthening procedures are generally performed only on the limbs. They often do not offer complete relief to the patient who may also have a smaller than normal thoracic cavity caused by undersized ribs.

Prognosis

Ellis-van Creveld syndrome is generally non-lethal with approximately two-thirds of those affected surviving to adulthood. Mortality is higher when the congenital heart defects associated with EvC syndrome are also present. Approximately half of those affected with Ellis-van Creveld syndrome with heart abnormalities die in childhood due to cardiorespiratory problems associated with these congenital heart defects or associated with pressure on the chest, primarily the lungs, caused by an underdeveloped rib cage. Of these, approximately one-half die within the first six months of life.

Resources

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ORGANIZATIONS

Ellis-Van Creveld Foundation. Farthingdale Farm, Hackmans Lane, Purleigh, Chelmsford, CM3 6RW. UK 01-621-829675. <http://www.cafamily.org.uk/Direct/e24.html>.

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937 info @geneticalliance. <http://www.geneticalliance.org>.

WEBSITES

Johns Hopkins Hospital Greenberg Center for Skeletal Dysplasias. <http://www.med.jhu.edu/Greenberg.Center/evc.htm>. (February 7, 2001).

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WebMD—Ellis-van Creveld syndrome. <http://webmd.lycos.com/content/asset/adam_disease_ellis-van_creveld_syndrome>. (February 7, 2001).

Paul A. Johnson

Emery-Dreifuss muscular dystrophy

Definition

Emery-Dreifuss muscular dystrophy (EDMD) is a rare childhood-onset degenerative muscle disease seen almost exclusively in males. Emery-Dreifuss muscular dystrophy is characterized by a classic triad of symptoms. These include early-onset contractures, very slow progressive muscle weakness and degeneration involving the upper arms and lower legs, and cardiac (heart) muscle disease.

Description

Emery-Dreifuss muscular dystrophy affects the arms, legs, spine, face, neck, and heart. This disease is characterized by contractures of the elbows and the Achilles tendons at an early age, slowly progressive muscle wasting and weakness, and life potentially life-threatening heart muscle disease. Intelligence is normal, however physical problems may be severe.

Symptoms and disease severity may vary between individuals. Three modes of **inheritance** exist: X-linked, autosomal dominant, and autosomal recessive. The symptoms of the autosomal dominant and X-linked forms of the disease are identical, however the autosomal dominant form appears to have a later onset of symptoms.

Genetic profile

Emery Dreifuss muscular dystrophy is inherited in different ways in different families. Most commonly EDMD is inherited in an X-linked recessive manner. Autosomal dominant inheritance of EDMD is also well characterized. As of early 2001 only one case of autosomal recessive inheritance of EDMD has been reported.

Rarely a new mutation causing EDMD can also occur, causing disease in a person with no family history. This is called a sporadic occurrence and is the ressult of a new change in a **gene** (new mutation) in that individual. New mutations account for approximately 10% of cases of EDMD.

X-linked recessive form

Emery-Dreifuss muscular dystrophy is usually inherited in an X-linked recessive manner. EDMD is the third most common type of X-linked muscular dystrophy. Symptoms begin in the first decade of life. A tendency to walk on the toes is often one of the first signs of EDMD. Muscle weakness first affects the lower extremities usually at age four or five.

X-linked diseases map to the human X chromosome, a sex chromosome. Females have two X **chromosomes**, whereas males have one X chromosome and one Y chromosome. Because males have only one X chromosome, they require only one X-linked disease gene to display disease. Since females have two X chromosomes, the effect of one X-linked recessive disease gene is masked by the disease gene's normal counterpart on the other X chromosome.

In classic X-linked inheritance all males are affected, presenting full clinical symptoms of the disease. Females are usually not affected. Affected fathers can never pass X-linked diseases to their sons. However, affected fathers always pass X-linked disease genes to their daughters. Females who inherit the faulty gene but do not show the disease are known as carriers. Female carriers of X-linked EDMD have a 50% chance to pass the disease-causing gene to each of their children.

It is unusual for female carriers of an X-linked disease to show symptoms of the disease. In X-linked EDMD, carrier females can exhibit certain symptoms of the disease. Females have two X chromosomes in each of their body cells. Very early on in fetal development, one X chromosome in each cell of a female is inactivated. The pattern of inactivation is random, so carrier females may express the disease-causing gene in some of their cells. An estimated 10–20% of female carriers of X-linked EDMD display varying symptoms of the disease. Female carriers can display the dangerous heart symptoms of EDMD. Less commonly, carrier females may show late-onset muscle weakness.

In 1994 it was recognized that the X-linked recessive form of Emery-Dreifuss muscular dystrophy is caused by changes, or mutations, in a gene now known as EMD or STA. This gene is located on the long arm of the human X chromosome at a location designated as Xq28. The STA gene is approximately 2,100 base pairs in length. This gene codes for emerin, an amino acid protein.

Emerin is an important protein normally found on the inner nuclear membrane of skeletal, cardiac, and smooth muscle cells as well as in other tissues. Emerin is missing from the nuclear membranes of males affected with X-linked EDMD. Emerin is not altered in other neuromuscular disorders.

Autosomal dominant form

In some families, Emery-Dreifuss muscular dystrophy may be inherited in an autosomal dominant pattern. Autosomal dominant EDMD is known as Emery-Dreifuss muscular dystrophy 2 (EDMD2), Hauptmann-Thannhauser muscular dystrophy, and Scapuloilioperoneal atrophy with cardiopathy. Autosomal dominant disorders affect both sexes equally. In autosomal dominant conditions a person, male or female, requires only one faulty gene to produce disease. There are no unaffected carriers of EDMD2. In families with EDMD2, both males and females can be affected and father to son inheritance of the disease can occur. Every child of a person affected with EDMD2 has a 50% chance of inheriting the disease.

In families with EDMD2, affected members exhibit a later onset of the same symptoms as someone affected with X-linked EDMD. Symptoms begin between the ages of 17 and 42. EDMD2 and X-linked EDMD are caused by changes in different genes on different chromosomes.

Muscle biopsy of people with EDMD2 are found to have normal emerin levels. In families with EDMD2, the disease is caused by changes, or mutations, in a gene known as Lamin A/C, or LMNA. Lamin A/C is located in a specific area on the long arm of chromosome 1 known as 1q21.2.

Lamin A/C codes for two proteins, lamins A and C. Like emerin, these lamins are associated with the nuclear

membrane. People with autosomal dominant EDMD2 have normal levels of emerin and low levels of these lamin proteins. Emerin and these lamins form an important protein complex in a cell's nuclear membrane. As of early 2001, the exact role of this complex is unclear. Scientists theorize that this important complex of proteins stabilizes the nuclear membrane and plays a role in regeneration of muscle fibers.

Autosomal recessive form

As of early 2001 a single case of autosomal recessively inherited EDMD has been documented. EDMD of autosomal recessive inheritance has been named Emery-Dreifuss muscular dystrophy 3 (EDMD3). For someone to be affected with an autosomal recessive disease they must inherit two copies of a disease-causing gene, one from each parent. A parent who has only one gene associated with autosomal recessive EDMD is not affected by the disease and is known as a carrier of the disease. Two carriers of autosomal recessive EDMD have a 25% chance to have a child affected with the disorder in each pregnancy.

Like EDMD2, EDMD3 is caused by mutations in the Lamin A/C gene located on the long arm of chromosome 1 at an area designated as 1q21.2. As of early 2001, the single known mutation associated with EDMD3 has not been found to also lead to EDMD2.

The single known patient with autosomal recessively inherited EDMD (EDMD3) displayed symptoms similar to those of X-linked and autosomal dominant EDMD without any heart involvement. He had difficulties when he started walking at 14 months of age. At five years of age, his contractures were so severe that he could not stand. At age 40, he was confined to a wheelchair and exhibited severe widespread muscle wasting. He displayed normal intelligence and did not have any heart problems. His carrier parents had no heart, skeletal, or muscle abnormalities.

Demographics

X-linked EDMD is estimated to occur in one in 100,000 births. EDMD2 and EDMD3 are far less common. As of early 2001, only one case of EDMD3 has been documented.

Only males exhibit full symptoms of X-linked EDMD. EDMD2 and EDMD3 may occur in males and females. X-linked EDMD and EDMD2 have been documented in many countries. There does not appear to be a single founder of these diseases, as many families have distinctly different backgrounds and different disease-causing mutations.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Signs and symptoms

Emery-Dreifuss muscular dystrophy is recognized by a classic triad of symptoms: contractures at a young age, progressive muscle weakness and degeneration involving the upper arms and lower legs, and cardiac (heart) muscle disease.

Contractures

Contractures, or frozen joints, are a hallmark of all forms of EDMD. A contracture is the abnormal shortening of a body part, usually a muscle or a tendon. This shortening creates joint deformity. Contractures usually begin in childhood or adolescence before any muscle weakness is evident. In most cases, contractures are recognized before patients reach 10 years of age.

Contractures may display as flexion or extension deformities. In a flexion contracture a muscle or tendon remains abnormally flexed, permanently bending a body part at a joint. In an extension contracture a muscle or tendon remains abnormally extended, not allowing a body part to bend at a joint. Affected persons cannot con-

trol these contractures and cannot release them at will. Contractures are treated with stretching, physical therapy, bracing, and surgery.

People affected with EDMD often have flexion contractures of the elbows and ankles. Elbow contractures force the elbow to remain bent at an angle. Contractures of the Achilles tendons, or heel cords, force the feet to remain in a pointed toe position. Children with EDMD often walk on their toes due to heel cord contractures. Neck and trunk contractures may also occur, restricting movement of the neck or the entire spine. **Scoliosis** is commonly found in patients with EDMD.

Muscle weakness and degeneration

Muscle weakness and degeneration are slowly progressive, affecting a distinct pattern of muscles. This pattern includes the muscles of the upper arms and the muscles of the lower legs. The biceps (inner upper arm), triceps (outer upper arm), tibialis anterior (inner lower leg), and peroneal (outer lower leg) muscles are commonly involved. Later, the muscles of the shoulder girdle and pelvic girdle, the shoulder and hip area muscles that stabilize and support the attachment of the arms and legs, may also be affected. Additionally, the highly specialized muscle of the heart is at risk for weakness and degeneration.

Heart disorders

Heart disease associated with EDMD may be life threatening. It is, however, potentially treatable. Not all patients with EDMD develop heart involvement. Any heart involvement often becomes apparent in the second to third decade of life. In rare cases heart problems may be the first symptom of EDMD. Early recognition of heart involvement is of utmost importance as surgical placement of a pacemaker may be life saving.

EDMD is associated with cardiac conduction defects (electrical impulse problems), heart muscle degeneration, and unusual tissues (abnormal fatty and fibrous tissues) growing into the heart. Conduction abnormalities can manifest as heart rhythm disturbances known as arrhythmias or, more seriously, heart block. Heart block is a dangerous situation where the heart is unable to respond correctly to its own electrical system. Arrhythmias and heart block can lead to fainting or even sudden death.

One uncommon type of heart conduction problem, total permanent auricular paralysis (TPAP), is relatively specific to EDMD. Scientists have found that 33% of 109 published cases of TPAP were due to EDMD.

The level of skeletal involvement in a patient with EDMD is not indicative of their level of heart involvement. Heart problems can be unpredictable, occasionally leading to sudden death without any prior symptom. In a review of 73 cases of X-linked EDMD, scientists found that 30 patients died suddenly between ages 25 and 39. Frequent careful checkups with a cardiologist (heart specialist) are necessary. Preventive surgical implantation of a pacemaker is often considered.

Female carriers of X-linked EDMD

Female carriers of X-linked EDMD may display some symptoms of disease. They can have the dangerous heart problems or, less commonly, muscle weakness. One case of sudden death of a female carrier of X-linked EDMD has been reported. It is recommended that female carriers of X-linked EDMD have regular examinations by a cardiologist.

Diagnosis

Diagnosis of EDMD is based on the classic triad of distinctive clinical symptoms seen in this disease. A diagnosis based on careful neuromuscular examination may be confirmed with muscle biopsy or DNA testing. Other special laboratory tests and neuromuscular tests may help physicians to confirm or rule out EDMD.

Creatine kinase (CK), a muscle enzyme, is often measured when symptoms of muscular dystrophy are present. CK levels are only mildly elevated in EDMD. Muscle biopsy can show microscopic changes in muscle fibers. Muscle biopsy also allows for a very practical test for X-linked EDMD where muscle tissue is stained with a chemical that binds specifically to emerin. If emerin is present, X-linked EDMD can be ruled out. If emerin is reduced or absent, X-linked EDMD is diagnosed.

Genetic testing and prenatal diagnosis for X-linked Emery-Dreifuss muscular dystrophy is available on a clinical basis. To perform DNA testing for X-linked EDMD a blood sample is required. This method of testing can diagnose female carriers of X-linked EDMD. Prenatal testing requires fetal cells obtained via **amniocentesis** or chorionic villus sampling. Once the specific alteration in the gene is identified in an affected family member, female relatives at risk to be carriers can be tested and prenatal diagnosis can be offered. Prenatal testing is performed on DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling.

Treatment and management

The muscle and skeletal symptoms of EDMD are treated as they appear. People with EDMD should see a neurologist at least once a year. Stretching and working with a physical therapist is useful in preventing or delay-

ing contractures. Occupational therapy can help patients adapt their activities and environment to their own particular needs. Ankle and foot braces are used to prevent leg deformity. Surgery may be necessary to release contractures. Exercise can help maintain muscle use and overall good health. Affected individuals may eventually require a wheelchair or other adaptive equipment.

Persons affected with EDMD require frequent, at least annual, heart checkups with a cardiologist. Heart symptoms can appear suddenly with disastrous consequences, so patients often have a pacemaker implanted before they have had any serious heart problem. Antiarrhythmia drugs, diuretics, ACE inhibitors, and blood thinners may help with some of the cardiovascular symptoms associated with EDMD. Heart transplant has been successful. Relatives of patients with EDMD, especially female carriers of X-linked EDMD, should also be offered yearly screening for heart involvement via electrocardiography and echocardiography.

Scientists are currently researching **gene therapy** as a possible treatment for EDMD. STA, the gene known to be involved in the X-linked form of EDMD, is a relatively small, less complicated gene. A small gene with a widespread product, such as STA, shows great promise for gene therapy.

Prognosis

Without serious heart involvement, most people with EDMD are expected to survive at least into middle age. Slow progression of muscle involvement allows most patients to walk and work until middle age or late adult life. Intellect is not affected.

Resources

BOOKS

Emery, Alan E. H. *Muscular Dystrophy: The Facts.* New York: Oxford University Press, Inc., 2000.

ORGANIZATIONS

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

WEBSITES

Gene Clinics. <http://www.geneclinics.org>.
Online Mendelian Inheritance in Man. <http://www3.ncbi.nlm.nih.gov/Omim>.

Judy C. Hawkins, MS

Emery-Dreifuss syndrome *see* **Emery-Dreifuss muscular dystrophy**

Encephalocele

Definition

An encephalocele is a defect characterized by the herniation of brain tissue and membranes through an opening in the cranium.

Description

Encephlaoceles are classified as neural tube defects, which are a group of disorders occurring due to the failure of closure of the neural tube at about week four of fetal development.

Other neural tube defects include **anencephaly** and **spina bifida**. Anencephaly results from failure of closure of the cranial end of the neural tube. This is a lethal condition. Spina bifida results from failure of neural tube closure in the spine. Spina bifida is a variable condition that is usually not lethal, but causes problems with bladder and bowel control and ambulation. It is usually associated with **hydrocephalus** (water on the brain), which can be treated with a shunt to drain the fluid into the body cavity. Encephalocele is the most rare neural tube defect.

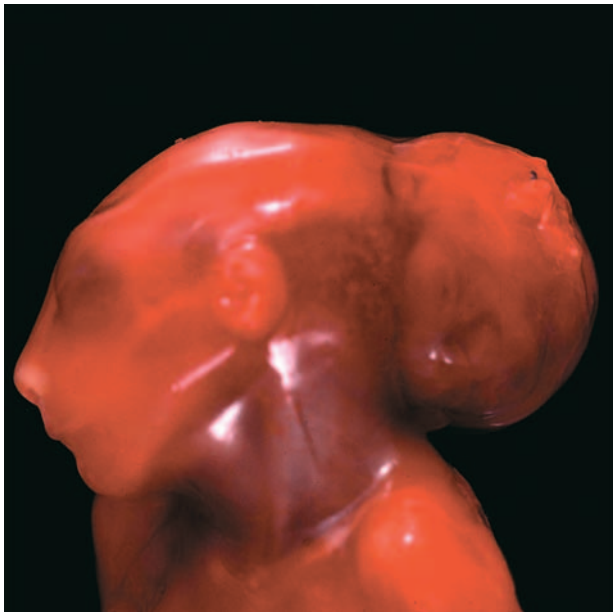
Encephaloceles are classified according to their location. Occipital (arising at the back of the head where the head meets the neck) encephaloceles occur in 75% of cases, parietal encephaloceles in 10%, and anterior encephaloceles (arising from the base of the nose) in 15%. AnterioPosterior encephaloceles have a poorer prognosis.

Genetic profile

The genetics of neural tube defects, including encephalocele, are not well understood.

Most encephaloceles are sporadic, following a multifactorial pattern (genetic and environmental factors involved) of **inheritance**. It is known that there is a genetic basis to encephaloceles and other neural tube defects, and it is believed that neural tube defects may be caused by different genetic factors in different subsets of families. Proof that genetic factors contribute to encephaloceles is that it is known to run in families, and it has been seen in association with some chromosome abnormalities. The number of genes and their location is still not known.

Occipital encephaloceles are associated with several single **gene** syndromes, including Meckle syndrome, dyssegmental dwarfism, Knobloch syndrome, Warburg syndrome, cryptophthalmos, and Voss syndrome. Anterior encephalocele may occur with frontonasal **dys-**



This 16 week old fetus has developed an encephalocele. The formation of the brain outside of the skull is visible. *(Custom Medical Stock Photo, Inc.)*

plasia. Encephalocele can also be seen in the amniotic band syndrome.

Demographics

The frequency of encephalocele has been reported to be between one in 2,000 to one in 5,000 live births. Anterior encephalocele is more common in Africa, Thailand, and India. Females outnumber males for occipital encephalocele but not other types.

The incidence of all neural tube defects is different in different parts of the world. It is highest in northern Europe, specifically the British Isles and especially South Wales. In the United States, it is higher on the East Coast than the West Coast.

The rate of sporadic neural tube defects in the general population is about one in 1,000. The rate is higher in areas with higher incidence. The chance for a recurrence of a neural tube defect after having an affected child is 2%. After two affected children the risk is 10%. The chance for an affected person to have an affected child is 4%. The chance for a second degree relative to have an affected child is 0.5%. Third degree relatives do not have an increased risk. Recurrence risks are given for neural tube defects as a group. A family with a previous child with anencephaly could have a child with spina bifida or encephalocele (the types do not "breed true" in families).

Care must be taken to be sure that the neural tube defect in the family was sporadic and not associated with a genetic syndrome, which would have a higher risk of recurrence.

Signs and symptoms

Symptoms of encephalocele may include hydrocephalus, spastic quadriplegia (paralysis of all four limbs), developmental delay, mental and growth retardation, uneven gait (ataxia), or seizures.

The size of the cerebral and skull abnormalities associated with encephaloceles are variable. Large encephaloceles are usually associated with microcephaly (abnormally small head). Microcephaly is usually associated with mental retardation.

Occipital encephalocele may be asymptomatic. If the ventricles are involved, hydrocephalus may occur. Anterior encephalocele may progress in size and may be solid, cystic, or both. There may be microcephaly and/or hydrocephaly, ocular hypertelorism (wide-spaced eyes), and cleft palate. There may be problems with vision, breathing, and feeding in patients with anterior encephaloceles. Many patients have mental retardation.

Diagnosis

Encephalocele can be diagnosed by ultrasound examination. Ultrasound examination is a screening test, the quality of which is affected by many factors including the machine used, skill of the operator, size and location of the lesion, and position of the fetus.

It is not likely that maternal serum alpha-fetoprotein testing (AFP) or **amniocentesis** would detect encephalocele. Alpha fetoprotein is a normal serum protein produced by the fetal liver. The AFP normally stays within the fetus, with a small amount present in the amniotic fluid from the fetal urine. When there is an "open" neural tube defect, there is a high amount of AFP in the amniotic fluid and the maternal serum. Although encephalocele is a neural tube defect, AFP testing on maternal blood or amniotic fluid only detects open neural tube defects. Encephaloceles are closed neural tube defects, meaning they are covered by a thick covering. This covering does not allow the AFP to leak into the maternal blood or the amniotic fluid in increased amounts that would be detected by the aforementioned tests. Pregnancies in which an encephalocele is diagnosed should be offered an amniocentesis and amniotic fluid biochemistry to better understand the cause of the abnormality.

CT scan can be used to determine the contents of the encephalocele once the baby is born. Some centers offer fetal MRI to attempt to classify the encephalocele prior to deliver. This is usually done at 22 weeks gestation.

Treatment and management

Nutrition, specifically defeciency of folic acid, has been implicated as causing an increased risk for neural tube defects. All women of childbearing age should take 0.4 mg of folic acid to reduce the risk of birth defects. Women with a previous child with a neural tube defect should take 4.0 mg of folic acid. This amount has been shown to reduce the recurrence risk for neural tube defects by 50%.

Prognosis

Size, location, and contents of the encephalocele determine the outcome for the child. Anterior encephaloceles have a much better prognosis than posterior. Mortality due to occipital encephalocele is reported as about 30% if hydrocephalus is present, and 2% if it is not. For all types of encephalocele with hydrocephalus, the mortality rate is 60%. Most patients with parietal encephalocele have associated brain malformations, and mental retardation occurs in 40%. Massive occipital encephalocele with microcephaly have a mortality rate of nearly 100%. Patients with encephaloceles that contain a single frontal lobe are more likely to have normal intelligence without hydrocephalus. Posterior have a poorer prognosis if they contain large amounts of the contents of the posterior fossa (an area of the brain at the back of the head), especially the brain stem. Complications such as hemorrhage or air embolism (stroke) can occur.

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Association of Birth Defects in Children. 930 Woodcock Rd., Suite 225, Orlando, FL 32803. (407) 895-0802. <http://www.biethdefects.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

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National Institute of Neurological Disorders and Stroke. <http://www.ninds.nih.gov/health_and_medical/disorders/encephaloceles>.

Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov/htbin-post/OMIM>.

Amy Vance, MS, CGC

Engelmann disease

Definition

Engelmann disease is a rare genetic condition that causes the long bones in the legs to become abnormally wide and may change the structure of other bones in the body. Its effects include bone pain (especially in the legs), skeletal disorders, and weak, underdeveloped leg muscles.

Description

Despite their strength and durability, human bones are living organisms. Throughout the life span, bones are constantly being broken down and rebuilt again without losing their proper size and shape. Diseases that interfere with this delicately orchestrated process (called bone remodeling) can produce pain and restrict our freedom of movement. In Engelmann disease, which was first described in 1920, the shafts of the long bones in the legs become thicker than normal. The femur (thigh bone) and tibia (shin bone) are primarily affected. These changes often cause severe bone pain and weak muscles in the legs. The weak, aching muscles associated with Engelmann disease may result in an unusual walk that resembles a "waddle." People with Engelmann may be bow-legged and have thin, elongated legs that look as if they are "wasting away."

Aside from bones in the leg, Engelmann disease can cause abnormal changes in other bones. People with Engelmann may develop **scoliosis** (in which the spine curves to the left or right side) or lumbar lordosis (a forward curvature of the spine). Engelmann disease can also cause bones to become abnormally hardened (a process referred to as sclerosis). This hardening can affect the bones at the base of the skull as well as those in the hands and feet. In rare cases, sclerosis may affect the jaw. Bone pain and aching, weak muscles may occur in parts of the body affected by the disease.

Engelmann can also affect internal organs and sight. The liver and spleen may become enlarged. Loss of vision may occur if bones near the eye sockets are affected. Some people with Engelmann report headaches, fatigue, and lack of appetite.

The underlying cause of Engelmann disease is unknown. It is often referred to in the medical literature as Camurati-Engelmann disease or progressive diaphyseal dysplasia (PDD). Less common names for the condition include osteopathia hyperostotica scleroticans and multiplex infantalis. Engelmann disease was sometimes referred to as ribbing disease in the past but this name is no longer used.

KEY TERMS

Endosteal—Relating to the endosteum, which is the lining of the medullary cavity.

Intracranial pressure—The pressure of the fluid between the brain and skull.

Medullary cavity—The marrow-filled cavity inside of a long bone (such as the femur).

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Periosteal—Relating to the periosteum, which is the connective tissue that covers all human bones.

Genetic profile

Engelmann is considered an inherited disease, though occasionally mutations may produce sporadic cases. It is passed from parent to child as an autosomal dominant trait. This means that a person may develop the condition after receiving just one copy of the abnormal **gene** (associated with Engelmann disease) from either the mother or father.

While the gene (or genes) responsible for Engelmann disease is still unknown, medical researchers have narrowed their search to a specific region of human **DNA**, which may eventually lead to identification. This chromosomal region is known as 19q13. A gene known as TGFB1 (transforming growth factor-beta 1), which plays a role in regulating bone growth, is located in this region and is therefore considered a possible candidate.

Demographics

Engelmann, which affects men and women equally, is a very rare disease that develops during childhood or young adulthood. It usually develops between ages four and ten, but may affect children as young as three months old. Other people may develop Engelmann disease anytime before age 30.

Signs and symptoms

The main symptoms of Engelmann disease are severe pain in the legs, weak and underdeveloped leg muscles, and a "waddling" walk. Other symptoms include bowed legs, unusually long limbs, spine problems such as scoliosis or lumbar lordosis, and flat feet. People with the disease may complain of headaches, lack of energy or appetite, vision problems, and an aching feeling in their hands and feet and, less often, in the jaw. Infants with Engelmann disease may experience feeding problems or a failure to thrive, and have a "malnourished" appearance.

In simple terms, Engelmann disease causes telltale changes in the structure of the femur and tibia, around the mid-shaft areas. Certain bone regions (specifically, the endosteal and periosteal surfaces) become abnormally thickened and hardened, which in turn narrows the medullary canal. Engelmann disease also causes the long bones to become "fusiform," a technical term indicating a tapered, spindle-like shape. In addition to these changes, Engelmann may cause abnormal hardening of other bones: in the hands and feet, at the base of the skull, and in the jaw. Engelmann may also involve liver and spleen enlargement, compression of the optic nerves, and increased intracranial pressure.

Diagnosis

Classic symptoms such as severe leg pain, underdeveloped leg muscles, and a "waddling" gait are often the first indication of the disease. An infant may initially experience feeding problems or failure to thrive (though these are more often the result of other, less serious problems). Imaging procedures such as a CT scan are used to detect the bone abnormalities associated with the condition, which mainly involve the thickening and sclerosis of the long bones of the legs. In some cases, x-ray studies of the skull are necessary. Blood tests and a biopsy of muscle tissue may be recommended.

In diagnosing Engelmann disease, a doctor must distinguish it from other conditions that produce similar symptoms, such as Paget's disease and certain types of **muscular dystrophy**.

Treatment and management

The treatment of Engelmann disease focuses on alleviating symptoms. While the changes in bone associated with the condition cannot be reversed, the use of steroid drugs such as cortisone or prednisone can ease bone pain and strengthen muscle. Surgery to repair muscles or bones is rarely necessary, while procedures to repair nerves in the eye are generally considered ineffective.

Prognosis

While Engelmann disease does not affect life expectancy, the prognosis for the condition varies. Some people affected by the disease are virtually free of symptoms; others are severely disabled. In some cases, the muscle weakness associated with Engelmann diminishes

or goes away completely with the passage of time. In other people, the effects of the disease seem to remain the same or slowly worsen during adulthood.

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National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse. One AMS Circle, Bethesda, MD 20892-3675. (301) 495-4484.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Greg Annussek

Epidermolysis bullosa

Definition

Epidermolysis bullosa (EB) is a group of rare inherited skin diseases that are characterized by the development of blisters following minimal pressure to the skin. Blistering often appears in infancy in response to simply being held or handled. In rarer forms of the disorder, EB can be life-threatening. There is no cure for the disorder. Treatment focuses on preventing and treating wounds and infection.

Description

Epidermolysis bullosa has three major forms and at least 16 subtypes. The three major forms are EB simplex, junctional EB, and dystrophic EB. These can range in severity from mild blistering to more disfiguring and life-threatening disease. Physicians diagnose the form of the disease based on where the blister forms in relation to the epidermis (the skin's outermost layer) and the deeper dermis layer.

KEY TERMS

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Dermis—The layer of skin beneath the epidermis.

Epidermis—The outermost layer of the skin.

Keratin—A tough, nonwater-soluble protein found in the nails, hair, and the outermost layer of skin. Human hair is made up largely of keratin.

Genetic profile

EB can be inherited as the result of a dominant genetic abnormality (only one parent carries the abnormal **gene**) or a recessive genetic abnormality (both parents carry the abnormal gene).

EB simplex results from mutations in genes responsible for keratin 5 and 14, which are proteins that give cells of the epidermis its structure. EB simplex is transmitted in an autosomal dominant fashion.

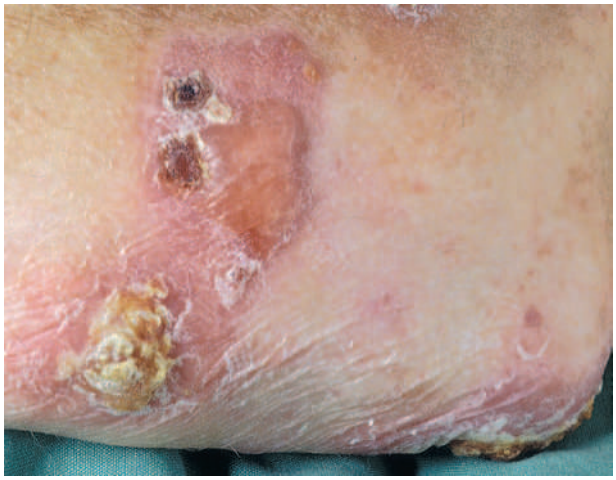
Dystrophic EB is caused by mutations in genes for type VII collagen, the protein contained in the fibers anchoring the epidermis to the deeper layers of the skin. The genetic mutations for junctional EB are found in the genes responsible for producing the protein Laminin-5. Dystrophic EB is an autosomal disorder and will only result if both parents transmit an abnormal gene during conception.

Demographics

The prevalence of epidermolysis varies among different populations. A study in Scotland estimated the prevalence to be one in 20,400. Researchers in other parts of the world estimate the prevalence to be one in 100,000. This variance is due to the variability of expression. Many cases of epidermolysis bullosa are often not accurately diagnosed and thus, are not reported.

Signs and symptoms

EB simplex, the most common form of EB, is the least serious form of the disease. In most affected individuals, the blisters are mild and do not scar after they heal. Some forms of EB simplex affect just the hands and feet. Other forms of EB simplex can lead to more wide-



Hemorragic blisters such as those seen on this patients arm form as a result of even slight trauma to the body for patients with epidermolysis bullosa. *(Custom Medical Stock Photo, Inc.)*

spread blistering, as well as hair loss and missing teeth. Recurrent blistering is annoying but not life threatening.

The second, or junctional, form of EB does not lead to scarring. However, skin on the areas prone to blistering, such as elbows and knees, often shrinks. In one variation of junctional EB, called gravis junctional EB of Herlitz, the blistering can be so severe that affected infants may not survive due to massive infection and dehydration.

The third form of EB, dystrophic EB, varies greatly in terms of severity, but more typically affects the arms and legs. In one variation, called Hallopeau-Siemens EB, repeated blistering and scarring of the hands and feet causes the fingers and toes to fuse, leaving them dysfunctional and with a mitten-like appearance.

Diagnosis

Physicians and researchers distinguish between the three major subtypes of EB based on which layer of the epidermis separates from the deeper dermis layer of the skin below. Patients suspected of having EB should have a fresh blister biopsied for review. This sample of tissue is examined under an electron microscope or under a conventional microscope using a technique called immunofluorescence, which helps to map the underlying structure.

Knowing that a family member has EB can help establish the diagnosis, but it is possible that parents or siblings will show no sign of the disease, either because it is caused by a new genetic mutation, or because the parents are carriers of the recessive trait and do not display the disease.

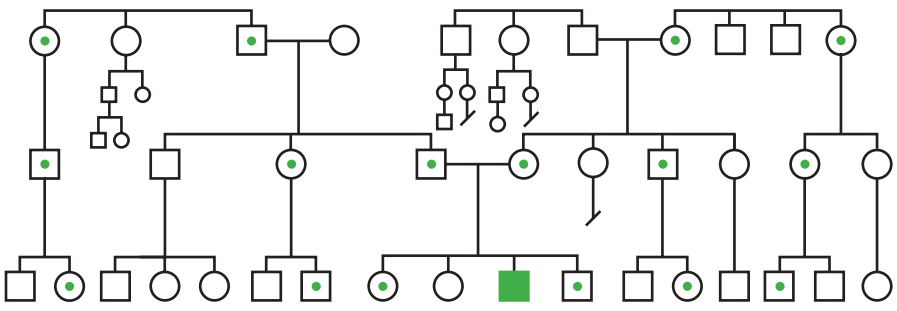
Treatment and management

The most important treatment for EB is daily wound care. Because the skin is very fragile, care must be taken to be certain that dressing changes do not cause further damage. Tape should not be applied directly to skin and bandages should be soaked off. Infection is a major concern, so a topical antibiotic, such as bacitracin, mupirocin, or sulfadiazine, should be routinely applied. Among persons with recessive dystrophic EB, the anticonvulsant phenytoin is sometimes effective because it decreases production of an enzyme that breaks down collagen.

Prognosis

The prognosis of EB varies depending on the subtype of the disease. Individuals with EB simplex can live

Epidermolysis bullosa, *letalis*



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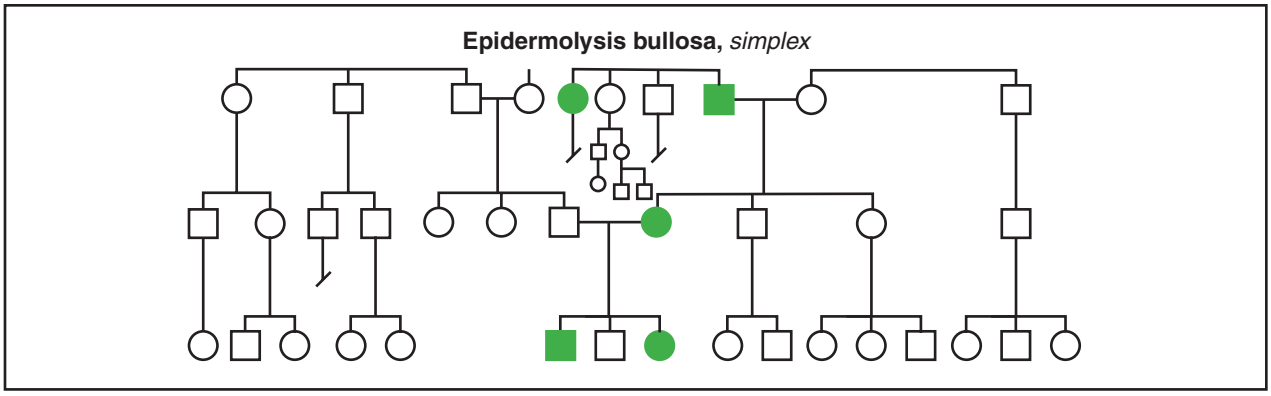

(Gale Group)

long, fulfilling lives. The severity of the junctional and dystrophic forms of EB can vary greatly. Infants affected with some forms of the disease often do not survive infancy; other forms can lead to severe scarring and disfigurement.

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Dystrophic Epidermolysis Bullosa Research Association of America (DebRA). 40 Rector St., Suite 1403, New York, NY 10006. (212) 513-4090. Fax: (212) 513-4099. staff.debra@exario.net. <http://www.debra.org>.

Dystrophic Epidermolysis Bullosa Research Association of United Kingdom, (DebRA). 13 Wellington Bus. Park, Dukes Ride, Crowthorne, Berkshire, RG45 6LS. UK 011-01344 771961. admin@debra.org.uk. <http://www.debra.org.uk>.

National Epidermolysis Bullosa Registry. University of North Carolina at Chapel Hill, Bolin Heights Bldg. #1, CB# 3369, Chapel Hill, NC 27514-3369. (919) 966-2007. Fax: (919) 966-7080. eb_registry@med.unc.edu. <http://www.med.unc.edu/derm/nebr_site>.

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L. Fleming Fallon, Jr., MD, PhD, DrPH

Epidermolysis bullosa junctionalis-disentis type *see* **Epidermolysis bullosa**

Epilepsy

Definition

Epilepsy is a chronic (persistent) disorder of the nervous system. The primary symptoms of this disease are periodic or recurring seizures that are triggered by sudden episodes of abnormal electrical activity in the brain. The term "seizure" refers to any unusual body functions or activities that are under the control of the nervous system.

Description

The word epilepsy is derived from the Greek term for seizure. Seizures can involve a combination of sensations, muscle contractions, and other abnormal body functions. Seizures may appear spontaneously—without any apparent cause—or can be triggered by a specific type of stimulus such as a flashing light. Specific cases of epilepsy may result from known causes, such as brain injury, or may have no apparent cause (referred to as *ideopathic epilepsy*). Ideopathic epilepsy may be initiated by a combination of genetic and environmental factors.

An epileptic seizure involves a transient (temporary) episode of abnormal electrical activity in the brain. During a seizure, many nerve cells within a specific region of the brain may begin to fire at the same time. This activity may then spread out over other parts of the brain. In addition to abnormal physical symptoms, seizures can bring on emotions ranging from fear, anger, and rage, to joy or happiness. During a seizure, patients may experience disorientation, spontaneous sensations of sounds, smells, visions, and distorted visual perception—such as misshapen objects and places.

Epilepsy can be caused by some event or condition that results in damage to the brain such as strokes, tumors, abscesses, trauma (physical injury), or infections such as meningitis. Epilepsy can also be triggered by inherited (genetic) factors or some form of injury or trauma at birth. Epilepsy cases that seem to have no readily identifiable cause are referred to as "idiopathic" cases in medical terminology. Symptoms of this disease can appear at any age. Seizures can damage and destroy brain cells and scar tissue can develop in the section of brain tissue where seizures originate.

There are many forms of epileptic seizures. The parts of the body that are affected by a seizure and the distinctive characteristics, duration, and severity of the symptoms can distinguish each type of epilepsy. Patients can experience more than one type of seizure. The nature of the symptoms depends on where in the brain the seizure originated and how much of the brain is involved. Seizures can be classified as either "generalized" or "partial". Partial seizures involve abnormal activity in a specific region of the brain.

Generalized (also called tonic-clonic) seizures last about two minutes and are the result of abnormal electrical activity that spreads out over both sides or hemispheres of the brain. They were formerly referred to as *grand mal* seizures. The patient will usually lose consciousness and fall during the episode. The term "tonic" refers to the first phase of a generalized seizure in which the body muscles become taunt or stiff. This is followed by strong, rhythmic muscular contractions (convulsions) of the "clonic" phase. Sometimes a patient's breathing may be hampered by a brief stoppage of the respiratory muscles, causing the skin to develop a bluish tinge due to lack of oxygen.

Epileptic seizures can also be classified as "complex" or "simple." Complex seizures generally involve a loss of consciousness, whereas simple seizures do not. Simple partial seizures can begin as a localized (focal) seizure and then evolve into a "secondary generalized" episode in which the initial abnormal electrical activity spreads to involve other parts of the brain. Patients may actually remember the physical and psychological events that occur during a simple seizure, such as the types of movement, emotions, and sensations, but frequently are completely unaware of the event. Partial seizures are more common in adults.

An "absence seizure" (once called *petit mal*) typically results in brief periods of "lack of awareness" and some abnormal muscle movement. The patient generally remains conscious during the seizure episode, but may become absent-minded and unresponsive. They may also appear to be "starring". Absence seizures last about 5–10 seconds.

How seizures affect a person's memory depends where in the brain seizures occur. Seizures can interfere with learning, storage, and retrieval of new information. For example, a form of epilepsy that produces seizures in the temporal lobe of the brain can cause a serious deterioration (loss) of memory function. Early treatment can help prevent or reduce memory loss.

In some forms of epilepsy, seizures can be triggered by a particular mental—or cognitive—activity. For example, the simple activity of reading aloud can trigger a seizure in patients with reading epilepsy. Symptoms include face muscle spasms. In medical terms, this type of epilepsy is referred to as "idiopathic localization-related epilepsy". This means that seizures occur in one part of the brain (in this case, the temporal lobes) and that there is no apparent cause that brought on the disease.

Genetic profile

Genetic factors contribute to about 40% of all epilepsy cases. Most of the generalized epilepsy syndromes and some of the partial epilepsy syndromes have an inherited component. Medical researchers suggest that at least 500 genes may somehow be involved in the development of various forms of epilepsy. It is believed that some of these genes can make people with epilepsy more susceptible or sensitive to environmental factors that initiate or start seizures. Only a few types of epilepsy are thought to be caused by just one type of **gene**.

Gene mutations can cause a variety of nervous system abnormalities that are associated with epilepsy. Different mutations may lead to abnormal brain development or progressive degeneration of brain tissue. Some gene mutations make nerve cells "hyperexcitable." These abnormal nerve cells can trigger outbursts of abnormal patterns of electrical activity that can initiate an epileptic seizure.

Specific gene locations (called gene markers) have been linked to various forms of the disease, such as juvenile myoclonic epilepsy. However, researchers have discovered that some individuals who possess this gene do not develop symptoms of this disease. In some pairs of identical twins with this gene, one twin may appear normal while the other develops typical symptoms of epilepsy. Thus, genetic **inheritance** seems to be just one of many factors that influence the possibility of developing epilepsy symptoms.

Some genetic mutations may also reduce the effectiveness of antiepileptic medication. One of the major goals of epilepsy research is to determine how a patient's genetic makeup can influence their drug therapy.

Demographics

Epilepsy affects about one percent of the population. Approximately 2.3 million Americans and 40 million people throughout the world have epilepsy. It is the second-most common neurological disorder. The highest incidence is in children under 10 and elderly over 70.

Signs and symptoms

Patients have little warning that they are about to experience an epileptic seizure. Some unusual feeling or "aura" which can act as a warning that an episode is about to start generally precedes actual seizures. An "aura" may take the form of an unusual sensation such as a fearful feeling, a mental image, or an unusual taste, smell, or sound. Some patients who do not experience seizures during the day or who have prolonged "auras" or warnings of an impending seizure can be permitted to drive. Getting a good night's sleep is a common problem for young children with epilepsy. Lack of sleep can then lead to behavior problems and constant drowsiness during the daytime. A stupor may follow a seizure.

KEY TERMS

Convulsion—Involuntary contractions of body muscles that accompany a seizure episode.

Ideopathic—Of unknown origin.

Lesion—A defective or injured section or region of the brain (or other body organ).

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Seizure—Any unusual body functions or activity that is under the control of the nervous system.

Diagnosis

Early symptoms of epilepsy include excessive staring, easy distraction, and difficulty in maintaining attention. To confirm the diagnosis, doctors look for neurological (nervous system) abnormalities such as speech or vision defects, defects in brain structure or other parts of the nervous system. The goal of the diagnositic testing is to identify where the seizures are originating. EEGs (electroencephalographs) are used to monitor electric activity— patterns of nerve impulses in the brain. A type of "brain scan" called MRI is also used extensively to try to pinpoint the location and type of abnormalities (referred to as lesions) in brain structure, which cause episodes of epileptic seizures. Idiopathic epilepsy—those cases for which no specific cause can be identified—are presumed to have a genetic basis.

Treatment and management

Currently, no cure exists for epilepsy. However, a wide range of treatment programs are available that provide varying degrees of success in controlling the symptoms of epilepsy.

Medication is the most effective and widely used treatment for the symptoms of epilepsy. Most medications work by interfering with or stopping the abnormal electrical activity in nerve cells that cause seizures. This form of treatment is generally referred to as anticonvul-

sant therapy. Medication is considered effective if the patient is free of seizures for at least one year.

Anticonvulsants are powerful drugs that can produce a variety of side effects, including nausea, fatigue, dizziness, and weight change. They can also increase the risk of birth defects, especially involving the early stages of embryonic development of the nervous system if taken during pregnancy.

Doctors prefer to put their patients on just one type of anticonvulsant drug. Some patients, however, experience more effective relief from their epilepsy symptoms by taking a combination of two different but "complementary" forms of medication. The choice of medication depends on the type of seizure that affects a patient, the patient's medical history—including response to other drug therapies, their age, and gender. For example, the drug Carbamazepine is one of the most effective medications and has little impact on important cognitive functions such as thinking, memory and learning.

Newer medications generally produce fewer side effects than their predecessors. Research into **gene therapy** may ultimately be the most effective form of epilepsy treatment, but is still in the very early stages.

Unfortunately, medication is ineffective for more than one third of known cases of epilepsy. More than 30% of patients with epilepsy cannot maintain adequate control of their seizures. Some genetic mutations may reduce the effectiveness of antiepileptic medications.

Surgery is recommended for some patients for whom medication cannot effectively control the frequency or severity of their seizures. Surgery is a treatment option only in extreme cases where doctors can identify the specific site in the brain where seizures originate. The most promising candidates for surgery are those with a single lesion on the temporal, frontal, or occipital lobes of the brain.

Prior to surgery, the patient must complete extensive testing to determine the precise patterns of seizures and to locate their point of origin in the brain. Patients spend extended stays in hospital during which their seizures are recorded on video and with the aid of EEGs. This machine records patterns of electrical activity in the brain using sensors (referred to as "electrodes") attached to various parts of the body.

The surgical procedure involves the removal of a small part of brain tissue in the "suspected" region. The anterior temporal lobe and hippocampus are the most common areas in which tissue is removed. In some studies, more than 83% of patients become free of seizures following surgery. Ninety-seven percent show significant improvement in their condition.

Vagus Nerve Stimulation (VNS) is another form of treatment for some cases of epilepsy that are unresponsive (referred to as "refractory epilepsy") to other forms of medical therapy. VNS may also be recommended for patients who cannot tolerate the side effects of medication. This procedure involves implanting a device that stimulates the Vagus nerve, located in the left side of the neck. In one study, this treatment reduced seizures by 78%.

A special dietary program is another treatment option for patients who are not good candidates for surgery or who have had little success with anticonvulsant medication. This form of treatment called the Ketogenic Diet can be effective for many types of epilepsy. It is most appropriate for young children whose parents can follow the rigid requirements of the diet. Older children and adults tend to have greater difficulty in sticking to the dietary rules for an extended period of time. The Ketogenic Diet is a stringent diet that is very high in fat, but low in proteins, carbohydrates, and calories. The excessive fat produces high levels of a substance called ketone (which the body makes when it breaks down fat for energy). Somehow these ketones help reduce the incidence of epileptic seizures. The success of this form of treatment varies. For some patients, the high fat diet is the best form of treatment. For others, the diet is less effective.

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Epilepsy Foundation. 4351 Garden City Drive, Landover, Maryland 20785. (800) 332-1000. <http://www.epilepsyfoundation.org>.

Epilepsy and Brain Mapping Program: Huntington Memorial Hospital. 10 Congress Street, Suite 505, Pasadena, California 91105. (800) 621-2102. e-mail: info@epipro.com, <http://www.epipro.com/meds.html>.

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Marshall G. Letcher, MA

Essential hypertension

Definition

Essential or primary hypertension, the most common form of hypertension, is elevated blood pressure that develops without apparent cause. Genetic factors, however, appear to play role in increasing the risk of developing the disorder.

Normal blood pressure refers to a range of values rather than a specific set of numbers and varies with factors such as age, race, and gender. However, a blood pressure reading greater than 140/90 mm Hg (millimeters of mercury pressure) is generally considered to be elevated. In this measurement, 140 refers to the systolic pressure (the maximum pressure in the arteries when the heart contracts). The 90 refers to the diastolic pressure (the lowest pressure in the arteries when the heart is between contractions).

Description

More than 95% of all elevated blood pressure can be classified as essential hypertension. When a disease, other physical problems, medications, or even temporary physical exertion or stress cause high blood pressure, the condition is called secondary hypertension.

Blood pressure refers to the force exerted by blood against the interior walls of the body's blood vessels. There are three categories of blood pressure, corresponding to the three types of blood vessels: arterial, capillary, and venous. In individuals with hypertension, arterial pressure (recorded as two numbers: systolic and diastolic pressure) is the most important measurement to obtain. The reason is that because of their relative proximity to blood flowing forcefully from the heart, arteries must withstand the highest pressures of all the body's blood vessels.

The body requires a relatively constant blood pressure level to ensure adequate passage of nutrients and oxygen to organs and tissues. To maintain a constant level of pressure, the body must balance and react to a number of factors such as these:

- volume of blood in the circulatory system
- amount of blood ejected by the heart (stroke volume
- heart rate
- thickness of the blood (viscosity
- elasticity of the arteries

When the systolic or diastolic pressure is elevated for an extended period of time, such as months or years, the heart has to work harder and may become damaged, along with the blood vessels. If it remains untreated, high blood pressure can lead to a variety of serious health problems, including heart disease, stroke, and kidney failure.

Genetic profile

Studies suggest that some people with essential hypertension may inherit abnormalities of the sympathetic nervous system—the part of the nervous system that controls heart rate, blood pressure, and the diameter of blood vessels. It is estimated that the risk of developing essential hypertension is increased two- to four-fold if one or both parents are diagnosed with the disorder.

Researchers have identified the **chromosomes** (11 and 18) that house the genes responsible for blood pressure regulation, although narrowing down the range of specific genes involved in hypertension is more difficult.

Genes under intense study are those that regulate a group of hormones known as the angiotensin-renin-aldosterone system. This system influences all aspects of blood pressure control, including blood vessel contraction, sodium and water balance, and cell development in the heart.

When blood pressure drops, the kidneys release an enzyme called renin, which initiates a chain reaction to bring blood pressure back up. Renin acts on angiotensinogen (a plasma protein) to produce the hormone, angiotensin I (an inactive form), which is then converted to angiotensin II (an active form of the hormone) by the angiotensin-converting enzyme (ACE). Angiotensin II then stimulates the adrenal glands to release the hormone aldosterone, which decreases kidney sodium excretion, thereby causing blood vessels to constrict. When blood vessels constrict, blood pressure goes up.

Researchers believe that this angiotensin-renin-aldosterone system evolved millions of years ago to pro-

KEY TERMS

Angiotensinogen—A plasma globulin (protein) formed in the liver and directly involved in the regulation of blood pressure.

Diastolic blood pressure—Blood pressure when the heart is resting between beats.

Renin—An enzyme produced by the kidneys.

Sphygmomanometer—An inflatable cuff used to measure blood pressure.

Systolic blood pressure—Blood pressure when the heart contracts (beats).

Vasodilator—A drug that relaxes blood vessel walls.

tect humans. By retaining salt and water and narrowing blood vessels, the body was ensured an adequate blood flow and the ability to repair injured tissue. Over time, however, this system outlived its original protective function and led to serious health complications.

Demographics

It is estimated that one in four Americans suffer from high blood pressure; it is also estimated that one in three people who have high blood pressure are unaware of the problem. Also, hypertension is much more common among African-Americans and Mexican-Americans than in Caucasian populations. Low levels of nitric oxide, which have been observed in individuals—particularly African-Americans—with elevated blood pressure, may be an important factor in the development of essential hypertension.

The prevalence of essential hypertension increases with age until at least the age of 80. Statistics indicate that more than half of all Americans over the age of 65 have hypertension. In those under the age of 55, essential hypertension is more common in males than females. Over age 55, there is an equal distribution among males and females.

Signs and symptoms

Essential hypertension may cause no symptoms for years. For this reason, high blood pressure is often called the "silent killer." The first symptom may be a heart attack or stroke. However, many people with hypertension may experience one or more of the following symptoms:

- headache
- dizziness
- blurred vision
- irregular or rapid heartbeat
- nosebleeds
- fatigue

Diagnosis

Although genetic studies hold hope for detecting, evaluating, and treating hypertension in the future, as of early 2001 there are no reliable genetic screening tests for the disorder. Thus, essential hypertension is a condition that cannot be diagnosed until it has developed; it is often diagnosed during a routine physical or medical examination.

Blood pressure is measured by an instrument called a sphygmomanometer. A cloth-covered rubber cuff is wrapped around the upper arm and inflated. When the cuff is inflated, an artery in the arm is squeezed to momentarily stop the flow of blood. Then the air is let out of the cuff, while a stethoscope placed over the artery is used to detect the sound of the blood spurting back through the artery. This first sound is the systolic pressure. The last sound heard as the rest of the air is released is the diastolic pressure. Both sounds are recorded on the mercury gauge of the sphygmomanometer.

Because a number of factors such as pain, stress, or anxiety can cause a temporary increase in blood pressure, hypertension is not diagnosed on the basis of one elevated reading. Also, blood pressure results may be different depending on which arm is used. Thus, if a blood pressure reading is 140/90 or higher for the first time, the physician will have the individual return for another blood pressure check. Diagnosis of essential hypertension is usually made based on two or more readings after the first visit.

A typical physical examination to evaluate hypertension includes:

- medical and family history (especially important to determine a genetic contribution)
- physical examination
- examination of the blood vessels in the eye
- chest x ray
- electrocardiograph (EKG)
- blood and urine tests

Treatment and management

There is no complete cure for essential hypertension because unlike secondary hypertension, there is no single

cause of the problem; it is a complex disorder only determined, in part, by genes. Environmental (lifestyle) factors interact with genetic factors to produce hypertension.

However, essential hypertension can be treated and managed effectively, even if an individual has a genetic predisposition to the disorder. If essential hypertension is mildly or even moderately high, it may be possible to bring it down to a normal level without medication. Weight loss, changes in diet, and exercise may be the only treatment necessary. General nonpharmacologic recommendations include:

- reducing the amount of salt (sodium) and fat in the diet
- exercising regularly
- maintaining a healthy weight
- limiting alcohol and caffeine consumption
- quitting smoking
- reducing stress through stress management techniques, relaxation exercises, or counseling

If lifestyle changes are not effective in lowering blood pressure to a normal level, medication may be prescribed. There are many types of drugs available to treat essential hypertension. The main categories of drugs include:

- diuretics (help kidneys eliminate excess salt and water from the body's tissues and blood, thereby reducing swelling and lowering blood pressure)
- beta-blockers, alpha-blockers, and alpha/beta blockers (act on nervous system to slow heart rate and reduce the force of the heart's contractions
- angiotensin-converting enzyme (ACE) inhibitors (block the production of substances that constrict blood vessels and reduce salt and water build-up in the tissues)
- calcium channel blockers (block the entry of calcium into muscle cells in artery walls, making arteries more relaxed)
- vasodilators (relax artery walls and lower blood pressure rapidly)
- peripheral acting adrenergic antagonists (act of nervous system to relax arteries and reduce the force of the heart's contractions)
- Centrally acting agonists (act on nervous system to relax arteries)

When a blood pressure medication is prescribed, it is important to:

- take the medication regularly, exactly as prescribed
- report any side effects immediately
- have regular follow-up visits with a physician

It may take weeks or even months to find the most effective pharmacologic treatment. Once an effective drug or combination of drugs is found, individuals with high blood pressure may require treatment for the rest of their lives.

Prognosis

The higher the blood pressure, the worse the prognosis. However, most serious complications of essential hypertension can be delayed or even avoided by getting regular blood pressure checks and by treating the disorder as soon as it is diagnosed.

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American Society of Hypertension. 515 Madison Ave., Suite 1212, New York, 10022. (212) 644-0600. <http://www.ash-us.org>.

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Genevieve T. Slomski, PhD

F

Fabry disease

Definition

Fabry disease is a genetic condition that typically affects males. It is caused by deficiency of an enzyme, a chemical that speeds up another chemical reaction. Fabry disease can affect many parts of the body including the kidneys, eyes, brain, and heart. Pain in the hands and feet and a characteristic rash are classic features of this disease.

Description

The symptoms of Fabry disease were first described by Dr. Johann Fabry and Dr. William Anderson in 1898. The enzyme deficiency that leads to the disease was identified in the 1960s. Fabry disease is caused by a change (mutation) in the GLA **gene**. This gene is responsible for the production of the enzyme alpha-galactosidase A. Alpha-galactosidase A normally breaks down globotriaosylceramide. Globotriaosylceramide is a natural substance in the body, made of sugar and fat. A mutation in the GLA gene leads to a decrease in alpha-galactosidase A activity which, in turn, leads to an excess of globotriaosylceramide. The excess globotriaosylceramide builds up in blood vessels (veins, arteries, and capillaries) and obstructs normal blood flow. It also builds up in parts of the skin, kidneys, heart, and brain. It is this build-up that inhibits normal function and leads to the symptoms associated with the disease.

The symptoms of Fabry disease are variable. Some individuals with Fabry disease have severe complications, while others have very mild symptoms. The first sign of the disease may be a painful burning sensation in the hands and feet (acroparesthesias). A red rash, most commonly between the belly button and the knees (angiokeratoma) is also common. The outer portion of the eye (cornea) may also become clouded in individuals with Fabry disease. The progressive buildup of globotriaosylceramide can also lead to kidney problems and heart disease in adulthood.

Genetic profile

The gene that produces alpha-galactosidase A is located on the X chromosome. It is called the GLA gene. Since the GLA gene is located on the X chromosome, Fabry disease is considered to be X-linked. This means that it generally affects males.

A person's sex is determined by his or her **chromosomes**. Males have one X chromosome and one Y chromosome. Females, on the other hand, have two X chromosomes. Males who possess a mutation or change in their GLA gene will develop Fabry disease. Females who possess a mutation in one of their GLA genes typically do not develop many of the symptoms associated with Fabry disease. This is because a female's other X chromosome does not have the mutation, and the normal chromosome can take over the function of the abnormal chromosome and keep her from getting the disease. These women are considered to be carriers. If a woman is a carrier, she has a 50% risk with any pregnancy to pass on her X chromosome with the mutation. Therefore, with every male pregnancy she has a 50% risk of having an affected son, and with every female pregnancy she has a 50% risk of having a daughter who is a carrier.

Demographics

Fabry disease affects approximately one in 40,000 live births. It occurs evenly among all ethnic groups. Almost always, only male children are affected. Although female carriers of the disease occasionally develop symptoms of the disease, it is rare for a female carrier to be severely affected.

Signs and symptoms

The signs and symptoms of Fabry disease vary. Some individuals with Fabry disease have many severe

KEY TERMS

Acroparesthesias—Painful burning sensation in hands and feet.

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Angiokeratoma—Skin rash comprised of red bumps. Rash most commonly occurs between the navel and the knees.

Blood vessels—General term for arteries, veins, and capillaries that transport blood throughout the body.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Cornea—The transparent structure of the eye over the lens that is continous with the sclera in forming the outermost protective layer of the eye.

Dialysis—Process by which special equipment purifies the blood of a patient whose kidneys have failed.

Enzyme replacement therapy—Giving an enzyme to a person who needs it for normal body function. It is given through a needle that is inserted into the body.

Left ventricular enlargement—Abnormal enlargement of the left lower chamber of the heart.

Mitral valve prolapse—A heart defect in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur, but there are usually no symptoms.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Proteinuria—Excess protein in the urine.

symptoms, while other individuals' symptoms may be few and mild. The symptoms typically increase or intensify over time. This progression is caused by the slow buildup of globotriaosylceramide as the person ages.

A painful burning sensation in the hands and feet (acroparesthesias) is one of the first symptoms of Fabry disease. This pain can be severe and may grow worse with exercise, stress, illness, extreme heat, or extreme cold. Another symptom of Fabry disease typically present during childhood is a red rash (angiokeratoma). This rash typically develops between the navel and the knees. Children with Fabry disease may also have a clouding of the outer most portion of the eye (cornea). This symptom is usually diagnosed by an eye doctor (ophthalmologist). The cloudiness may increase with time. A decreased ability to sweat is another common symptom of Fabry disease.

Due to the progressive nature of Fabry disease, most affected individuals develop additional symptoms by 40 years of age. The buildup of globotriaosylceramide in the heart can lead to heart problems. These heart problems can include changes in the size of the heart (left ventricular enlargement), differences in the heart beat, and leaky heart valves. Mitral valve prolapse is a particular type of leaky heart valve that is common in Fabry disease, even in childhood. The excess globotriaosylceramide can also disrupt normal blood flow in the brain. In some cases this can cause dizziness, seizures, and stroke. The kidneys are other organs affected by Fabry disease. Kidney problems can lead to an abnormal amount of protein in the urine (proteinuria). Severe kidney problems can lead to kidney failure.

Although the symptoms of Fabry disease usually occur in males, female carriers may occasionally exhibit symptoms of the disease. Some carriers experience pain in their hands and feet. Carrier females may also have proteinuria and clouding of their cornea. It is rare for a female to experience all of the symptoms associated with Fabry disease.

Diagnosis

Initially, the diagnosis of Fabry disease is based on the presence of the symptoms. It should also be suspected if there is a family history of the disorder. The diagnosis of Fabry disease is definitively made by measuring the activity of the alpha-galactosidase enzyme. When the activity is very low, it is diagnostic of Fabry disease. This enzyme analysis can be performed through a blood test. Measuring the activity of the enzyme can also detect a female carrier. Women who are carriers of Fabry disease have enzyme activity that is lower than normal.

Prenatal diagnosis is possible by measuring the alpha-galactosidase A activity in fetal tissue drawn by **amniocentesis** or chorionic villus sampling (CVS). Fetuses should be tested if the mother is a carrier. A woman is at risk of being a carrier if she has a son with Fabry disease or someone in her family has Fabry disease.

Treatment and management

There is currently no cure for Fabry disease. However, there are clinical trials underway in which individuals with Fabry disease are being given the alpha-galactosidase A enzyme as a form of enzyme replacement therapy. If successful, this enzyme replacement therapy may reduce or eliminate the symptoms associated with Fabry disease.

Until the enzyme replacement therapy is proven to be safe and effective, individuals with Fabry disease must rely on traditional treatments. Individuals with Fabry disease are recommended to have routine evaluations of the their heart and kidneys. Some individuals with kidney disease require a special diet that is low in sodium and protein. Dialysis and kidney transplantation may be necessary for patients with severe kidney disease. Certain medications may reduce the risk of stroke. Finally, individuals with Fabry disease are recommended to avoid the situations that cause the pain in their hands and feet to grow worse. In some situations medication may be required to reduce the pain.

Prognosis

The prognosis for individuals with Fabry disease is good, especially with the arrival of enzyme replacement therapy. Currently, affected individuals survive into adulthood, with the symptoms increasing over time.

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Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

Deptartment of Human Genetics, International Center for Fabry Disease. Box 1497, Fifth Ave. at 100th St., New York, NY 10029. (866) 322-7963. <http://www.mssm.edu/genetics/fabry>.

Fabry Support and Information Group. PO Box 510, 108 NE 2nd St., Suite C, Concordia, MO 64020. (660) 463-1355. <http://www.cpgnet.com/fsig.nsf>.

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Holly Ann Ishmael, MS, CGC.

Faciopalatoosseous syndrome *see* **Otopalatodigital syndrome**

Facioscapulohumeral muscular dystrophy *see* **FSH muscular dystrophy**

Factor V deficiency *see* **Factor V leiden thrombophilia**

Factor V Leiden thrombophilia

Definition

Factor V Leiden thrombophilia is a common genetic disorder that leads to a predisposition or increased chance to develop blood clots in the veins (venous thrombosis).

Description

Factor V Leiden thrombophilia is a disorder caused by an inherited change or mutation in the genetic instructions for making a substance called factor V. The factor V change leads to an increased chance to develop blood clots in blood vessels.

Blood clots form in two steps. In the first step, the body produces platelets that are "sticky" and can form initial plugs or clots when needed. However, the first platelets only form the first temporary plugs. To form a more lasting plug or clot the platelets release chemicals to attract more platelets and other substances called clotting factors (or clotting proteins). In the second step, the platelets come together with the clotting proteins and

form fibers. The fibers weave together and make the clot stronger and longer lasting.

Individuals affected by factor V Leiden thrombophilia have a genetic mutation that makes a longer lasting, "stickier" form of the clotting factor or protein called factor V. This different form of factor V is called factor V Leiden. The factor V Leiden clotting protein lasts longer in the blood because a chemical produced by the body called Activated Protein C (or APC), which is supposed to help "break-down" the factor V clotting protein, cannot break down the factor V Leiden clotting protein as easily and quickly as it breaks down normal factor V. The factor V Leiden clotting protein breaks down 10 times slower than an average clotting factor V and accordingly stays in the blood longer.

Since there is longer lasting, extra sticky Factor V Leiden in the blood, individuals affected by factor V Leiden thrombophilia have an increased chance to have free-floating blood clots (thrombosis) that can get stuck in the veins and other blood vessels. An alternative name used to describe this condition is Hereditary Resistance to Activated Protein C.

Genetic profile

Factor V Leiden thrombophilia occurs when a specific **gene** on the long arm of chromosome one is changed or mutated. This gene is called *F5*. Every person has approximately 30,000–35,000 genes that tell our bodies how to form and function. Each gene is present in pairs, since one is inherited from the mother, and one is inherited from the father. Depending on the inheritance of the changed or mutated *F5* gene, factor V Leiden thrombophilia runs in families in a more severe and less severe form.

The less severe form of factor V Leiden thrombophilia is called "heterozygous" and occurs when an individual inherits only one copy of the altered or mutated gene that causes factor V Leiden. The more severe form of factor V is called "homozygous" and is caused by the inheritance of two non-working or mutated copies of the gene that causes factor V Leiden thrombophilia.

Heterozygous factor V Leiden is inherited in an autosomal dominant pattern. In an autosomal dominant condition, only one changed or mutated copy of the gene for a particular condition is necessary for a person to experience symptoms of the condition. If a parent has an autosomal dominant condition, there is a 50% chance for each child to have the same or similar condition. In heterozygous factor V Leiden thrombophilia, the chance of being affected by venous blood clots is four to eight times greater than the general population.

Homozygous factor V Leiden thrombophilia is inherited in an autosomal recessive pattern. An autosomal recessive condition is caused by the inheritance of two changed or mutated copies of a gene. Individuals who are affected by heterozygous factor V Leiden thrombophilia have only one copy of the altered gene. However, when two people with heterozygous factor V Leiden thrombophilia have children together, there is a 25% chance, with each pregnancy, for the child to inherit two copies, one from each parent. That child then has two altered copies of the gene and therefore, has homozygous factor V Leiden thrombophilia. When an individual inherits two non-working copies of the gene that lead to homozygous factor V Leiden thrombophilia, there is an up to 80 times increased risk to be affected by blood clots stuck in the veins (venous thrombosis). Additionally, most individuals affected by homozygous factor V Leiden thrombophilia develop blood clots at a younger age than individuals affected by heterozygous factor V Leiden thrombophilia.

Demographics

Factor V Leiden thrombophilia is the most common inherited form of increased blood clotting in the general population. Factor V Leiden thrombophilia is more common in the Caucasian population. In the general U.S. and European population, heterozygous factor V Leiden thrombophilia occurs in approximately three to eight individuals per 100. In the same general U.S. and European population, homozygous factor V Leiden thrombophilia affects approximately one in 5,000 individuals. The frequency in African Americans, Asian Americans, Hispanic Americans, and Native Americans is smaller than that of Caucasian Americans, but is still present at approximately 0.45–2% of individuals tested. Factor V Leiden thrombophilia is very rare in individuals who have only Asian, African, and indigenous Australian descent.

Signs and symptoms

The symptoms of factor V Leiden thrombophilia vary. Some affected individuals have no physical problems. Other individuals will have complications including blood clots blocking blood vessels (thromboembolism), deep vein thrombosis, unexplained multiple miscarriages and stillborn infants, gall bladder dysfunction, strokes, and heart attacks. The most common physical sign of factor V Leiden thrombophilia is thromboembolism (a blockage in the veins caused by a free floating clot [embolus]). Venous thromboembolism is most common in the deep veins of the legs (deep venous thrombosis or DVT of the legs). Since non-specific and common factor

V Leiden thrombophilia is suspected in individuals who have had multiple blood clots in the veins (venous thrombosis), more than three unexplained miscarriages, or a family history of individuals with multiple blood clots in the blood vessels.

Diagnosis

Diagnosis of factor V Leiden thrombophilia can be done through a blood coagulation screening test or DNA analysis of the gene that codes for factor V.

The blood coagulation screening test uses the breakdown protein APC in a resistance study to see how quickly the factor V is broken down as compared to other blood clotting factors. An individual with factor V Leiden thrombophilia has factor V that is resistant or much slower to being broken down by the APC protein. At this time there are two types of APC resistance screening tests for factor V Leiden thrombophilia. The preferred test is the "modified second generation" APC resistance study because an extra step in the testing (dilution by plasma without factor V) makes it almost 100% accurate even in pregnant women and patients being treated by medications such as heparin and warfarin.

The DNA or molecular analysis examines the *F5* gene to learn if the gene is altered or mutated.

Prenatal diagnosis is not offered routinely because the disorder is fairly mild and effective treatment is available.

Treatment and management

The treatment and management of individuals affected by factor V Leiden thrombophilia is focused on prevention of floating blood clots (thrombosis) and thromboembolism. The management of affected individuals should be overseen by a hematologist who specialized in blood clotting disorders and a general practitioner or internist who can work closely with the hematologist.

At different times of life, different specialists may need to be added. For example, when pregnant, a perinatologist or high-risk obstetrician should work with the hematologist during pregnancy. Additionally, individuals who have had a deep vein clot or stroke may need to consult a vascular specialist and/or neurologist.

The physicians managing an affected individual's care should discuss with them the timing, risks, and benefits of taking birth control pills and taking "blood thinning" anticoagulant medications like warfarin, aspirin, and heparin. Individuals affected by factor V Leiden thrombophilia should also be examined to make sure they do not have other blood clotting disorders in addition to factor V Leiden thrombophilia.

KEY TERMS

Deep vein thrombosis—A blood clot in one of the systemic veins deep in the body.

Heterozygous—Having two different versions of the same gene.

Homozygous—Having two identical copies of a gene or chromosome.

Thromboembolism—A condition in which a blood vessel is blocked by a free-floating blood clot carried in the blood stream.

Venous thrombosis—A condition caused by the presence of a clot in the vein.

Prognosis

Individuals affected by factor V Leiden thrombophilia have a wide range of symptoms and signs. Some individuals affected by factor V Leiden thrombophilia will never develop physical signs and symptoms of the disorder. Other individuals will be more severely affected. Most affected individuals will not experience their first clotting event until adulthood. However, individuals with homozygous factor V Leiden thrombophilia have a significantly increased risk to have symptoms of the disease at a younger age. Treatment and close management of the disorder can reduce the risk of thromboembolism significantly.

Resources

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ORGANIZATIONS

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"Factor V Leiden Thrombophilia." *GeneClinics.* <http://www.geneclinics.org/profiles/factor-v-leiden/index.html>.

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Dawn A. Jacob, MS

Fahr disease

Definition

Fahr disease is a rare, progressive neurological disorder that is often hereditary. Characterized by deposits of calcium in the basal ganglia and other parts of the brain, Fahr disease causes worsening **dementia** and the loss of routine motor skills, among other symptoms.

Description

Though calcium is important for good health, this mineral can have harmful effects when it appears in parts of the body where it does not belong. In Fahr disease, abnormal deposits of calcium build up in a region of the brain called the basal ganglia (mainly in a section called the globus pallidus), as well as in other parts of the brain. The basal ganglia is the technical name given to clusters of nerve cells that help to initiate and control movements of the body—for example, reaching for a cup of coffee or taking a step forward while walking. The presence of these calcium deposits (referred to as calcifications) interferes with the working of the brain, causing a variety of debilitating mental and physical symptoms that worsen over time. Aside from the basal ganglia, the calcium deposits associated with Fahr disease often appear in other areas of the brain such as the cerebral cortex.

Two important effects of the disease are dementia and the loss of learned motor skills. People affected by Fahr disease may become overly forgetful and easily confused or disoriented. They have trouble performing relatively simple tasks that require basic hand-eye coordination. Most people with the disease experience slurred speech and problems involving involuntary movements or poor coordination. In addition, personality changes and disorders of mood may develop. In one study of 18 people with Fahr disease, half of the participants had symptoms of obsessive-compulsive disorder, major **depression**, or **bipolar disorder**. People with Fahr may have psychotic symptoms, including hallucinations (visual and auditory), a distorted perception of reality, and paranoid delusions.

As the disease progresses, it causes an increasing degree of paralysis. Muscles become stiff and physical movement is restricted. Aside from these symptoms, people with Fahr disease may experience specific movement disorders: slow, twisting movements of the hands and feet (athetosis) and jerky, rapid movements that resemble spasms (chorea). Vision may also be affected. Because the disease can weaken nerves that carry signals from the eyes to the brain, people with Fahr disease may experience partial or almost complete vision loss. Ear infections have also been reported.

The underlying cause of Fahr disease is unknown. For this reason, it is described as an idiopathic disorder. Fahr disease is often referred to in the medical literature as idiopathic basal ganglia calcification (IBGC). Less common names for the disease include cerebrovascular ferrocalcinosis, non-arteriosclerotic cerebral calcifications, and striopallidodentate calcinosis.

Genetic profile

Fahr disease often runs in families and is believed to be inherited either as a recessive or dominant trait. In the recessive version of Fahr disease, a person must inherit the same abnormal **gene** (associated with Fahr disease) from both parents in order to develop the disease. Therefore, a child who receives only one recessive gene for the disease can become a carrier but will not usually develop symptoms. In the dominant version of Fahr disease, a person may develop the condition after receiving just one copy of the abnormal gene from either the mother or father.

Researchers studying a particular family affected by Fahr disease over several generations discovered a pattern regarding the age at which the condition strikes. The results of this medical study indicated that each generation with Fahr developed symptoms at an earlier age than previous generations, a phenomenon described as "genetic anticipation." The family (referred to as a "kindred") being analyzed in this study was affected by the dominantly inherited version of the disease.

While studying this kindred, researchers located a gene believed to play a role in the disorder. The gene was named IBGC1 ("IBGC" is short for "idiopathic basal ganglia calcification," another name for Fahr disease). The gene location was identified as 14q, situated on the long arm (called q) of chromosome 14. Despite this finding, more research is necessary to determine the identity and nature of the gene or genes associated with Fahr disease.

Aside from inherited forms, Fahr disease can occur sporadically for reasons that are not well understood. Some medical studies suggest that sporadic cases of Fahr disease may result from an as-yet unidentified infection that affects the fetus in the womb.

Demographics

Fahr disease, which appears to affect men and women equally, can appear at any stage of life, from infancy to adulthood. Some people diagnosed with the disease have no family history of the condition, while in many cases Fahr disease runs in families and affects members of several generations. In people with dominantly inherited Fahr disease, symptoms usually appear

anywhere between the ages of 30 and 60. The recessive form of Fahr disease emerges at a younger age, between infancy and young adulthood.

Signs and symptoms

People with Fahr disease have abnormal calcium deposits in the basal ganglia, primarily in the globus pallidus region, and often in other parts of the brain. Loss of brain cells in these areas also occurs. The results of electrocardiogram (ECG) studies, which monitor heartbeats, are often abnormal in people with Fahr disease. Other signs include malfunctioning parathyroid glands and low blood calcium levels.

The disease causes a variety of physical and psychological symptoms. The head of a person with Fahr disease is often smaller and rounder than normal. The condition causes worsening dementia and loss of routine motor skills. Muscle stiffness, movement disorders, and paralysis may occur. Speech often becomes slurred. In some cases, Fahr disease causes vision problems and ear infections. Symptoms of Parkinson's disease may develop as well.

Diagnosis

In simple terms, Fahr disease is diagnosed when calcifications in the basal ganglia are associated with slurred speech, movement disorders, and other specific symptoms. Special imaging procedures such as a CT scan can detect the presence of calcium deposits. Symptoms can be determined by physical and psychological examinations. Friends or family members with relevant observations of the patient's behavior can also be helpful. Blood tests may be recommended to evaluate blood calcium levels and the parathyroid glands. The appearance of Parkinson-like symptoms is not essential to a diagnosis of Fahr disease.

In the absence of other factors, calcium deposits in the basal ganglia do not necessarily indicate the presence of Fahr disease. Such calcifications may be due to a metabolism disorder, infectious disease, or a genetic disorder other than Fahr disease. In fact, sometimes these calcifications may be present without producing any symptoms or harmful effects, especially in people older than age 60.

Treatment and management

There is no cure for Fahr disease, which worsens over time. The process of calcification cannot be stopped or reversed. Where possible, clinicians focus on alleviating its various mental and physical effects. These may vary to some degree depending on the individual, even among members of the same family. Lithium carbonate, for example, may be recommended to control psychotic symptoms, while antidepressant medications are often used to combat depression. Ear infections associated with Fahr disease can be treated with antibiotics and pain medication.

KEY TERMS

Calcification—A process in which tissue becomes hardened due to calcium deposits.

Cerebral cortex—The outer surface of the cerebrum made up of gray matter and involved in higher thought processes.

Cerebrum—The largest section of the brain, which is responsible for such higher functions as speech, thought, vision, and memory.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

Idiopathic—Of unknown origin.

Neurological—Relating to the brain and central nervous system.

Parathyroid glands—A pair of glands adjacent to the thyroid gland that primarily regulate blood calcium levels.

Prognosis

Due to its damaging effects on the brain and nervous system, Fahr disease is eventually fatal.

Resources

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ORGANIZATIONS

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

Association of Birth Defect Children, Inc. <http://www.birthdefects.org>.

Greg Annussek

Familial adenomatous polyposis

Definition

Familial adenomatous polyposis is an inherited condition that typically presents with extensive adenomatous polyps of the colon. These polyps often develop into **colorectal cancer** in early adult life. Other symptoms are often present as well. These signs include polyps in the upper gastrointestinal tract, malignancies in the brain or thyroid, pigmented retinal lesions, and osteomas.

Description

Familial adenomatous polyposis (FAP) was first clearly described as a dominantly inherited colorectal cancer susceptibility by Lockhart-Mummery in an article published in 1925. FAP has since served as a paradigm for hereditary cancer and has taught much about the diagnosis, surveillance, and management of colon cancer. It is one of the most clearly defined and well understood of the inherited colon cancer syndromes. FAP is thought to account for approximately 1% of all cases of colorectal cancer.

FAP is a disorder that is characterized by the development of hundreds to thousands of glandular colorectal tumors called adenomas or adenomatous polyps, meaning that they are benign growths made of the tissue that lines the inside of the colon. They are described as polyps because they protrude from mucous membranes. In FAP, these tumors generally develop by the second or third decade of life. They are found in the internal lining of the colon and the rectum, with a particular affinity for the left side of the colon or the rectosigmoid. By themselves, these polyps are benign but they have the ability to become malignant, leading to colorectal cancer. If the polyps are not treated properly, it is almost certain that a person affected with FAP will develop colorectal cancer by the age of 40.

Other clinical findings that may be associated with FAP include polyps in the upper gastrointestinal tract, extraintestinal manifestations such as osteomas and epidermoid cysts, desmoid formation, retinal lesions, and malignant changes in other organs. Symptoms are thought to manifest anywhere between the ages of 16 and 50 years.

FAP is also known as familial polyposis coli (FPC) and adenomatous polyposis coli (APC). Gardner syndrome and Turcot syndrome are variants of FAP. Gardner syndrome is used to describe patients with FAP and the extracolonic symptoms of osteomas, soft tissue tumors, desmoids, and dental abnormalities. Turcot syndrome is used when FAP is seen in conjunction with tumors of the central nervous system called medulloblastomas (cerebral tumors that occur in childhood). Attenuated FAP (AFAP) is another variant of FAP. In this condition, individuals present with fewer polyps, usually fewer than 100 in number and often in the right colon. Patients with AFAP may have a later onset of cancer than those with classic FAP.

Genetic profile

FAP is inherited in an autosomal dominant pattern; thus, an affected person has a 50% chance of passing the disease on to each of his or her children. It is almost 100% penetrant, meaning that nearly everyone who carries the **gene** mutation will show signs of the disorder. The majority of patients with FAP inherit the mutation from one of their parents. However, in approximately 25% of cases, there is no family history of the disorder and FAP occurs because of a new mutation in the affected individual.

The majority of cases of FAP are due to mutations of the APC gene, located on the long arm (or "q" arm) of chromosome 5. This gene encodes a protein that is important in cell adhesion and signal transduction. More than 300 different APC mutations have been described in FAP patients. Most APC mutations seen in individuals with FAP result in translation of a protein that is shorter than normal. This shortened protein cannot function properly.

Studies have shown that the type and location of the APC mutation seems to correlate to the clinical symptoms that a person manifests. For example, if the muta-

tion is located near the center of the gene, colonic polyps tend to be more dense and numerous. A mutation towards the ends of the gene often leads to polyps that are fewer and more sparse, as in attenuated FAP. Additionally, mutations at one particular end (the 3′ end) of the APC gene seem to be associated with a higher risk of desmoid formation. However, it is known that family members who carry identical mutations often have different clinical features. This suggests that modifying genes and/or environmental factors also influence the expression of the APC **gene mutation**.

The APC gene is a tumor suppressor gene, meaning that its function is to control cell growth. When APC is mutated, it does not function correctly and allows cells to grow out of control. This results in tumors that may lead to cancer. Carriers of mutations in APC inherit a germline mutation in one allele of the gene. Thus, in every one of their cells, one gene does not make the APC protein but the corresponding gene on the other chromosome continues to produce the functional protein. Thus, tumor suppression continues. However, if a somatic mutation occurs in the remaining functional gene, no APC protein is made, tumor suppression fails, and tumors develop. These somatic mutations occur in various parts of the body at various times, leading to multiple tumors forming in distinct parts of the body over a period of time. In the case of FAP, many of these tumors are confined to the colon but can occur in other organs as well.

Demographics

Approximately one of 8,000 people are affected with FAP. It is seen in all racial and ethnic groups. Both sexes are affected equally.

Signs and symptoms

Colorectal

FAP is characterized by multiple (more than 100) adenomatous polyps of the colon and rectum. These generally develop after the first decade of life but the age of onset of adenomas is variable. Fifteen percent of individuals with FAP will show these polyps by age 10, 75% by age 20, and 90% by the age of 30. More than 95% of affected individuals will have adenomatous polyps by the age of 35. Although these polyps are benign, it is inevitable that, if left untreated, at least one of the hundreds of polyps will eventually progress to cancer. The majority of cancers appear by the age of 40 and over 90% appear by the age of 45. Symptoms of polyps and/or colorectal cancer may include rectal bleeding, change in bowel habits, iron deficiency anemia, or abdominal pain.

KEY TERMS

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Duodenum—Portion of the small intestine nearest the stomach; the first of three parts of the small intestine.

Epidermoid cyst—Benign, cystic tumor derived from epithelial cells.

Fibroma—A non-malignant tumor of connective tissue.

Hypertrophy—Increase in the size of a tissue or organ brought on by the enlargement of its cells rather than cell multiplication.

Lipoma—A benign tumor composed of well-differentiated fat cells.

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

Osteoma—A benign bone tumor.

Somatic—Relating to the nonreproductive parts of the body.

Upper gastrointestinal tract

Many individuals with FAP will develop adenomas in the upper gastrointestinal tract as well. The second portion of the duodenum is particularly prone to these polyps. These adenomas are benign, as they are in the colon, but about 5–8% of patients with FAP will eventually develop cancer in this area. Duodenal cancer seems to cluster in certain FAP families while being absent in others. Adenomas of other portions of the small bowel may also occur but with lesser frequency.

In people affected with FAP, benign adenomas can also be seen in the stomach. Gastric cystic fundic gland polyps are also common. These are benign polyps that occur in the fundic gland of the stomach, an organ that secretes enzymes and mucus. It is rare for these polyps to become cancerous in individuals of Western origin. However, in Japanese and Korean families with FAP, the risk of gastric cancer is reported to be increased three- to four-fold over the general population.

Ocular, skeletal, and cutaneous

Approximately two thirds of individuals with FAP will have congenital hypertrophy of the retinal pigment epithelium (CHRPE). These lesions are typically flat, oval, and pigmented. They can be detected by an oph-

thalmology examination. In FAP patients, these lesions are usually multiple, bilateral, or large. CHRPE does not affect vision nor does it have the potential to become malignant. However, CHRPE is a very important finding for families with a history of FAP. If CHRPE runs in a family with FAP, all or nearly all affected individuals in the family will have this finding. It can be detected at birth and can thus identify susceptible family members at a young age.

Other manifestations of FAP include dental abnormalities, such as impacted teeth, supernumerary teeth, and congenitally missing teeth. Osteomas can occur, often in the jaw area or on the forehead. Soft tissue tumors, such as lipomas, epidermoid cysts, and fibromas, are observed in some patients with FAP as well.

Other tumors and malignancies

Abdominal desmoid tumors occur in approximately 15% of individuals with FAP. Desmoids are tumors made of connective tissue. Although they are not cancerous, approximately 10% grow very aggressively and can become life threatening. They may lead to obstruction of blood vessels, the intestine, or ureters. They may also result in abdominal distention and associated pain and discomfort. Over 70% of these tumors develop in women aged 20–40 years, suggesting a hormonal role in their development. Additionally, they occur more commonly in those who have had prior abdominal surgery. Desmoids may occur as part of classical FAP, as part of Gardner syndrome, or sporadically, without the colonic findings of FAP.

Additionally, patients with FAP are at an increased risk for cancers in organs outside of the gastrointestinal tract. These include brain tumors, thyroid tumors, and hepatoblastoma. Hepatoblastoma is a malignant tumor of the liver and occurs in approximately 1.6% of patients with FAP in the first five years of life. Tumors of the adrenal cortex, biliary tract, and pancreas have also been reported.

Diagnosis

FAP can be diagnosed clinically in any individual with greater than 100 polyps in the colon or rectum. The diagnosis is usually made via flexible sigmoidoscopy. This procedure may be done on a routine basis or to investigate possible symptoms of colon polyps and/or colorectal cancer. Flexible sigmoidoscopy involves inspecting the interior of the rectum and the sigmoid colon, or the terminal part of the colon that leads to the rectum. Once polyposis has been established, complete colonoscopy may be necessary to further evaluate the extent of the polyps. Colonoscopy is a more invasive procedure that examines the interior of the entire colon and rectum, rather than only the terminal part.

In regards to a diagnosis in someone who does not yet have colon polyps, retinoscopy, or examination of the retina, can be useful in a family where CHRPE has been associated with FAP. In these families, CHRPE is almost 100% predictive of FAP; thus, if someone shows CHRPE on an ophthalmology exam, it is very likely that he or she is affected with FAP. Although **genetic testing** yields more certain predictive information, retinoscopy is a relatively inexpensive and noninvasive alternative diagnostic screening measure in families with a history of FAP associated with CHRPE.

Polyps may be first detected by the passage of occult (non-visible) blood in the stool by means of fecal occult blood testing. This testing is also inexpensive and noninvasive, and if positive, could indicate that additional testing is needed.

FAP can also be diagnosed by genetic testing. This type of testing may be used to identify someone who is affected but does not yet show any symptoms of FAP. It can also confirm the diagnosis of FAP in someone who has polyposis discovered via flexible sigmoidoscopy. APC gene testing is most commonly performed by using a protein truncation test, which looks for the presence of shortened proteins caused by a mutation in the gene. This test identifies approximately 80% of those affected with FAP. The other 20% of patients likely have mutations that do not lead to a shortened protein. It is important to test an affected family member first to determine whether or not a detectable mutation is present. If a mutation is identified in this affected person, other at-risk family members can be tested for this particular mutation. However, if a mutation is not identified in the affected individual, it is likely that the mutation does not produce a shortened protein. In this case, protein truncation testing would not be informative for the rest of the family.

FAP can also be diagnosed by linkage analysis. This testing identifies approximately 95% of affected individuals, however, blood samples are required from numerous family members, including at least one affected individual. Thus, logistically, this procedure is more complicated than the protein truncation testing mentioned above.

Treatment and management

There is no treatment for FAP because the genetic abnormality cannot be fixed. Management focuses on routine surveillance of at-risk and affected individuals for early detection and treatment of colonic polyps and other manifestations.

For individuals diagnosed with FAP, either clinically or via linkage analysis or protein truncation testing, an annual sigmoidoscopy must be performed beginning around the age of 10 years. Sigmoidoscopy is preferred because it is less invasive, safer, and will generally detect the polyps in FAP, since they are numerous and located throughout the colon. Colonoscopy may be the screening tool of choice if attenuated FAP is suspected since, in this case, the adenomas are fewer in number and may be confined to the proximal region of the colon.

If polyposis is established, complete colonoscopy may be necessary to determine the extent of the polyposis and the timing of surgery. As for surgical intervention, total proctocolectomy (removal of the colon and rectum) is generally favored. In some cases, however, other options may be explored, such as total colectomy (removal of the colon only) with ileorectal anastomosis (the small intestine is attached to the upper portion of the rectum). Another option, a total colectomy with rectal mucosal protectomy and ileoanal anastomosis, involves removing the entire colon and mucosal lining of the rectum. The ileum then attaches to the anus. Fecal continence is preserved since the muscular wall and the sensory functions of the rectum are preserved.

All FAP patients require an annual medical examination with palpation of the thyroid and review of systems. Children with FAP should be screened for hepatoblastoma with liver palpation. In some cases, hepatic ultrasonography and determination of serum alpha-fetoprotein levels can be helpful as well. Upper endoscopy (visual examination of the upper GI tract) should be completed every one to four years to evaluate for gastric and duodenal polyps. Duodenal polyps that increase in size or number or show signs of becoming cancerous may require treatment. This treatment may include evaluation by computed tomography or ultrasonography. If necessary, the polyps may be removed by laser or other procedures.

For at-risk relatives of affected individuals, regular screening should begin between the ages of 10 and 12 years. This screening can be accomplished by protein truncation testing. If the test result is a true negative (i.e., negative result in a person whose affected relative had a positive result), further screening is debatable. This test result should theoretically eliminate the risk of FAP but, in very few cases, laboratory errors or other circumstances may lead to an inaccurate test result. Thus, some experts suggest that flexible sigmoidoscopy should be performed at ages 18, 25, and 35 years in these individuals, with standard screening thereafter.

After colectomy, continued surveillance of patients with FAP is advised. Ileoscopy is recommended every three to five years. This procedure examines the ileum, or lowest third of the small intestine, and serves to rule out polyps, which may become cancerous with time. Surgical removal of desmoid tumors is invasive but often necessary to prevent reoccurrence. Various nonoperative treatments have been attempted, such as medication and radiation, none of which have yielded consistent results. Additionally, the examination of any remaining rectal tissue by proctoscopy is necessary every six months to assess for signs of rectal cancer.

As with any abdominal surgeries in people affected with FAP, there is a risk of developing desmoid tumors after the colectomy. If desmoids are suspected, computed tomography is the recommended imaging study. MRI may also be used in certain cases.

Surveillance of the upper GI tract, even after total proctocoloectomy, is appropriate due to the incidence of tumors in this area previously discussed.

Prognosis

Without colectomy, the prognosis for individuals with FAP is very poor. Patients who have not undergone colectomy develop colorectal cancer at an average age of 39 years. The majority of untreated people die from colorectal cancer by the age of 42 years. For those who do undergo a colectomy, prognosis is variable, depending on development and progression of other tumors. For example, desmoids can also be detrimental to those affected with FAP, accounting for 11–31% of all mortality in these individuals.

Resources

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Olson, Sharon J., and Kristin Zawacki. “Hereditary Colorectal Cancer.” *Clinical Genetics* 35, no. 3 (September 2000): 671–685.

ORGANIZATIONS

Colon Cancer Alliance. 175 Ninth Ave. New York, NY 10011. (212) 627-7451. <http://ccalliance.org>.

Colorectal Cancer Network. PO Box 182, Kensington, MD 20895-0182. (301) 879-1500. <http://www.colorectal-cancer.net>.

Hereditary Colon Cancer Association (HCCA). 3601 N 4th Ave., Suite 201, Sioux Falls, SD 57104. (800) 264-6783. <http://hereditarycc.org>.

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Mary E. Freivogel, MS

Familial dysautonomia

Definition

Familial dysautonomia (FD) is a rare inherited disorder in which affected individuals experience multiple malfunctions of the autonomic nervous system (the part of the nervous system that regulates heart muscle, smooth muscle, and glands) as well as the sensory, motor, and central components of the nervous system. The disorder is progressive with a continual loss of nerve cells of the sensory and autonomic nervous systems.

Description

Familial dysautonomia is an inherited disorder that occurs almost exclusively in people of Eastern European (Ashkenazi) Jewish descent. FD is one of a larger group of at least five hereditary sensory and autonomic neuropathies (HSANs), meaning conditions that stem from abnormalities of the nervous system. FD was first described in 1949 by pediatricians Conrad Riley and Richard Day. They reported five children, all Jewish, who had an unusual set of reactions to mild anxiety, attributed to a disturbance of the autonomic nervous system. FD is also known as HSAN type III or Riley-Day syndrome. Decades of studies have determined the cause to be a genetic abnormality that causes poor development of nerve cells in the fetus, leading to a progressive loss of nerve cells of the autonomic and sensory nervous systems. The depletion of nerve cells in the autonomic system causes problems with unstable heart rate, blood pressure, and body temperature, as well as gastrointestinal dysfunction, poor motor coordination, and emotional instability. Abnormal development of the sensory nervous system results in poor perception of pain, heat, and cold. This causes affected individuals to injure themselves without being aware of it. This deterioration of the nervous system worsens throughout life and causes multiple health problems that lead to the death of 50% of those affected by adulthood.

Genetic profile

FD is caused by mutations (genetic errors) in the IKBKAP **gene** that is found on human chromosome 9, specifically located at region 9q31. The disease is inherited as an autosomal recessive trait. This means that both parents have one copy of the mutant gene but do not have the disease. For these parents, there is a 25% chance with each pregnancy that the child will have the disease.

The IKBKAP gene has two known mutations, which together account for 100% of the Ashkenazi Jewish (AJ) cases of FD. There is also a third mutation causing FD that is rarely seen in the non-AJ population. This mutation's gene location has not yet been determined.

Demographics

The abnormal gene causing FD is rare in the general population but has a fairly high incidence in the Ashkenazi Jewish population, originating from Eastern Europe. Both males and females are affected. In the at-risk group, one in 30 people is thought to be a carrier of the abnormal gene, with a disease frequency of one in 3,600 live births. Rare non-Jewish individuals affected with FD have been reported.

Signs and symptoms

Sensory and autonomic nervous systems fail to develop properly in the fetus. Newborn babies with FD have poor or decreased muscle tone and have poor sucking and swallowing reflexes that make feeding difficult. Affected babies are prone to periods of abnormally low body temperature and are unable to produce adequate tears when crying.

Although symptoms vary markedly, by adolescence affected children have a 90% likelihood of spinal curvature and experience weakness and leg cramping. They have difficulty concentrating and undergo personality changes including negativism, **depression**, irritability, and insomnia. Forty percent of affected people have regular vomiting crises in response to either emotional or physical stress. A crisis typically involves one to three days of compulsive vomiting, rapid heart rate, high blood pressure, profuse sweating, and red, blotchy skin.

Between crises, affected individuals may experience low blood pressure when rising to a standing position. They often have unexplained fevers and may have convulsions in response to even mild infections. Uncoordinated swallowing, reflux of stomach contents, and a poor gag reflex result in food or fluids being misdirected into the trachea and lungs. Aspiration pneumonia (lung infections) often follows. Kidney function may deteriorate with age. Affected people have an abnormal

response to low oxygen or high carbon dioxide in their blood. They do not experience the expected "air hunger," or urge to breathe, and may faint or have a seizure. Lack of tears, decreased blink frequency, and insensitivity of the eye to pain from foreign objects can cause inflammation and ulcers of the cornea.

A characteristic sign in those affected with FD is a lack of the sense of taste. This is due to the absence of taste buds on the tongue. Other sensory problems include an inability to feel pain or distinguish between hot and cold temperatures; sensory loss increases with age. Deep tendon reflexes in affected individuals are decreased. Poor speech and motor coordination result in abnormal gait, unsteadiness, tongue thrusting, and abnormal rhythmic facial movements. Growth is stunted, with an average adult height of 5 ft (1.5 m). Puberty is delayed in both sexes. However, fertility and offspring of affected individuals are normal.

Diagnosis

The presentation of FD varies between affected people. However, of the many manifestations of the disease, five signs are key to the diagnosis:

1. flat, smooth tongue due to lack of taste buds,
2. lack of red flare following histamine injection under the skin,
3. decreased or absent deep tendon reflexes,
4. absence of overflow tears with emotional crying,
5. parents of Ashkenazi Jewish background.

Other frequent signs are decreased response to pain and temperature, decreased corneal reflexes, unstable blood pressure, low blood pressure when standing erect, red blotching of the skin, and increased sweating. Further supportive evidence of the FD diagnosis are feeding difficulties, repeated aspiration pneumonia, episodes of low body temperature, breath holding spells, poor muscle tone, delayed motor development, repeated vomiting, spinal curvature, and poor growth. Prenatal diagnosis, screenings for carrier status, and **genetic counseling** are available.

Treatment and management

The identification of the FD gene as IKBKAP was reported in March 2001, and is expected to lead to new treatment approaches as the function of the gene is better understood. Until that time, treatment is preventive and supportive. Management of vomiting crises is attempted with drugs, replacement of body fluids, prevention of aspiration of stomach contents into lungs, control of blood pressure, and promotion of sleep. Care of the eyes includes artificial tears, eyewashes, and topical antibiotics to avoid ulcers of the cornea. Early and adequate treatment of even mild infections is important to avoid triggering vomiting crises. Children should be protected from injury and watched for any unusual swellings or skin discolorations as a way of coping with decreased pain and temperature perception.

Physical and occupational therapy, braces, and other orthopedic aids are used for spinal curvature and poor motor coordination. Speech therapy, special feeding techniques, and respiratory care enhance quality of life. It is important to maintain adequate fluid intake and avoid situations such as high elevations, air travel, and diving underwater where oxygen concentration is decreased. Psychological intervention is helpful to alleviate emotional instability and mood swings in children and depression, anxiety, and phobias in adults.

Prognosis

The disease process of familial dysautonomia can not be prevented at present but 80% of affected individuals survive beyond childhood and 50% reach age 30. With the 2001 determination of the exact location of the gene abnormality, prospects for new treatments and possible **gene therapy** are on the horizon.

KEY TERMS

Aspiration pneumonia—Lung infection due to food or liquids accidentally getting into lungs.

Autonomic nervous system—The part of the nervous system that regulates heart muscle, smooth muscle, and glands.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

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Marianne O'Connor, MT (ASCP), MPH

Familial endocrine adenomatosis *see* **Multiple endocrine neoplasia**

Familial fatal insomnia *see* **Prion diseases**

Familial infiltrative fibromatosis *see* **Hereditary desmoid disease**

Familial Mediterranean fever

Definition

Familial Mediterranean fever (FMF) is an inherited disorder of the inflammatory response characterized by recurring attacks of fever, accompanied by intense pain in the abdomen, chest, or joints. Attacks usually last 12–72 hours, and can occasionally involve a skin rash. Kidney disease is a serious concern if the disorder is not treated. FMF is most prevalent in people of Armenian, Sephardic-Jewish, Arabic, and Turkish ancestry.

Description

FMF could be described as a disorder of "inappropriate" inflammation. That is, an event that in a normal situation causes a mild or unnoticeable inflammation might cause a severe inflammatory response in someone with FMF. Certain areas of the body are at risk for FMF-related symptoms. A serosa is a serous (fluid-producing) membrane that can be found inside the abdominal cavity (peritoneum), around the lungs (pleura), around the heart (pericardium), and inside the joints (synovium). The symptoms of FMF are due to inflammation of one or more of the serosal membranes (serositis). Thus, FMF is also sometimes called recurrent polyserositis.

During an attack, large numbers of neutrophils, a type of white blood cell, move into the affected areas causing painful inflammation and fever. These episodes may be accompanied by a skin rash or joint pain. In a few cases, chronic arthritis is a problem. Amyloidosis is a potentially serious condition in which proteins called amyloids are mistakenly produced and deposited in organs and tissues throughout the body. Left untreated, amyloidosis often leads to kidney failure, which is the major long-term health risk in FMF.

In most cases, the attacks of fever and pain are first noticed in childhood or adolescence. The interval between these episodes may be days or months, and is not predictable. However, during these intervals people with FMF typically lead normal lives. It is not entirely clear what brings on an attack, but people with FMF often report mild physical trauma, physical exertion, or emotional stress just prior to the onset of symptoms. Treatment for FMF involves an oral medication called colchicine, which is highly effective for the episodes of fever and pain, as well as for amyloidosis and the kidney disease that can result from it.

FMF is most common in certain ethnic groups from the eastern Mediterranean region, but cases in other ethnic groups in other parts of the world are increasingly being reported. FMF is also known by many other names. They include: recurrent hereditary polyserositis, benign paroxysmal peritonitis, familial paroxysmal polyserositis, paroxysmal polyserositis, familial recurrent polyserositis, periodic fever, periodic amyloid syndrome, periodic peritonitis syndrome, Reimann periodic disease, Reimann syndrome, Siegel-Cattan-Mamou syndrome, and Armenian syndrome.

Genetic profile

FMF is a genetic condition inherited in an autosomal recessive fashion. Mutations in the MEFV **gene** (short for Mediterranean Fever) on chromosome number 16 are the underlying cause of FMF. Autosomal recessive **inheritance** implies that a person with FMF has mutations in both copies of the MEFV gene. All genes come in pairs, and one copy of each pair is inherited from each parent. If neither parent of a child with FMF has the condition, it means they carry one mutated copy of the MEFV gene, but also one normal copy, which is enough to protect them from disease. If both parents carry the same autosomal recessive gene, there is a one in four chance in each pregnancy that the child will inherit both recessive genes, and thus have the condition.

The MEFV gene carries the instructions for production of a protein called pyrin, named for pyrexia, a medical term for fever. The research group in France that co-discovered the protein named it marenostrin, after ancient Latin words that referred to the Mediterranean Sea. The movement of neutrophils into an area of the body where trauma or infection has occurred is the major cause of inflammation, which is a normal process. Research has shown that pyrin has some function in controlling neutrophils. In a situation where minor trauma or stress occurs, some initial inflammation may follow, but a functional pyrin protein is responsible for shutting-down the response of neutrophils once they are no longer needed. An abnormal pyrin protein associated with FMF may be partly functional, but unstable. In some instances, the abnormal pyrin itself seems to be "stressed," and loses its ability to regulate neutrophils and inflammation. Left unregulated, a normal, mild inflammation spirals out of control. Exactly what causes pyrin in FMF to lose its ability to control neutrophils in some situations is not known.

Demographics

Estimates of the incidence of FMF in specific eastern Mediterranean populations range from one in 2,000 to one in 100, depending on the population studied. Specific mutations in the MEFV gene are more common in certain ethnic groups, and may cause a somewhat different course of the disease. A few mutations in the MEFV gene likely became common in a small population in the eastern Mediterranean several thousand years ago. It is postulated that carrying a single copy of a mutated gene produced a modified (but not abnormal) inflammatory response that may have been protective against some infectious agent at that time. Those who carried a single "beneficial" mutation in the MEFV gene were more likely to survive and reproduce, which may explain the high carrier frequency (up to one in five) in some populations. People of Armenian, Sephardic-Jewish, Arabic, and Turkish ancestry are at greatest risk for FMF. However, a better understanding and recognition of the symptoms of FMF in recent years has resulted in more reports of the condition in other ethnic groups, such as Italians and Armenian-Americans.

Signs and symptoms

The recurrent acute attacks of FMF typically begin in childhood or adolescence. Episodes of fever and painful inflammation usually last 12–72 hours. About 90% of people with FMF have their first attack by age 20. The group of symptoms that characterizes FMF includes the following:

KEY TERMS

Acute phase reactants—Blood proteins whose concentrations increase or decrease in reaction to the inflammation process.

Amyloid—A waxy translucent substance, composed mostly of protein, that forms plaques (abnormal deposits) in the brain.

Amyloidosis—Accumulation of amyloid deposits in various organs and tissues in the body such that normal functioning of an organ is compromised.

Colchicine—A compound that blocks the assembly of microtubules—protein fibers necessary for cell division and some kinds of cell movements, including neutrophil migration. Side effects may include diarrhea, abdominal bloating, and gas.

Leukocyte—A white blood cell. The neutrophils are a type of leukocyte.

Leukocytosis—An increase in the number of leukocytes in the blood.

Neutrophil—The primary type of white blood cell involved in inflammation. Neutrophils are a type of granulocyte, also known as a polymorphonuclear leukocyte.

Pericarditis—Inflammation of the pericardium, the membrane surrounding the heart.

Peritonitis—Inflammation of the peritoneum, the membrane surrounding the abdominal contents.

Pleuritis—Inflammation of the pleura, the membrane surrounding the lungs.

Pyrexia—A medical term denoting fevers.

Serositis—Inflammation of a serosal membrane. Polyserositis refers to the inflammation of two or more serosal membranes.

Synovitis—Inflammation of the synovium, a membrane found inside joints.

Fever

An FMF attack is nearly always accompanied by a fever, but it may not be noticed in every case. Fevers are typically 100–104°F (38–40°C). Some people experience chills prior to the onset of fever.

Abdominal pain

Nearly all people with FMF experience abdominal pain at one point or another, and for most it is the most common complaint. The pain can range from mild to

severe, and can be diffuse or localized. It can mimic appendicitis, and many people with undiagnosed FMF have had appendectomies or exploratory surgery of the abdomen done, only to have the fever and abdominal pain return.

Chest pain

Pleuritis, also called pleurisy, occurs in up to half of the affected individuals in certain ethnic groups. The pain is usually on one side of the chest. Pericarditis would also be felt as chest pain.

Joint pain

About 50% of people with FMF experience joint pain during attacks. The pain is usually confined to one joint at a time, and often involves the hip, knee, or ankle. For some people, however, the recurrent joint pain becomes chronic arthritis.

Myalgia

Up to 20% of individuals report muscle pain. These episodes typically last less than two days, and tend to occur in the evening or after physical exertion. Rare cases of muscle pain and fever lasting up to one month have been reported.

Skin rash

A rash, described as erysipelas-like erythema, accompanies attacks in a minority of people, and most often occurs on the front of the lower leg or top of the foot. The rash appears as a red, warm, swollen area about 4–6 in (10–15 cm) in diameter.

Amyloidosis

FMF is associated with high levels in the blood of a protein called serum amyloid A (SAA). Over time, excess SAA tends to be deposited in tissues and organs throughout the body. The presence and deposition of excess SAA is known as amyloidosis. Amyloidosis may affect the gastrointestinal tract, liver, spleen, heart, and testes, but effects on the kidneys are of greatest concern. The frequency of amyloidosis varies among the different ethnic groups, and its overall incidence is difficult to determine because of the use of colchicine to avert the problem. Left untreated, however, those individuals who do develop amyloidosis of the kidneys may require a renal transplant, or may even die of **renal failure**. The frequency and severity of a person's attacks of fever and serositis seem to have no relation to whether they will develop amyloidosis. In fact, a few people with FMF have been described who have had amyloidosis but apparently no other FMF-related symptoms.

Other symptoms

A small percentage of boys with FMF develop painful inflammation around the testes. Headaches are a common occurrence during attacks, and certain types of vasculitis (inflammation of the blood vessels) seem to be more common in FMF.

Diagnosis

Individually, the symptoms that define FMF are common. Fevers occur for many reasons, and nonspecific pains in the abdomen, chest, and joints are also frequent ailments. Several infections can result in symptoms similar to FMF (Mallaret meningitis, for instance), and many people with FMF undergo exploratory abdominal surgery and ineffective treatments before they are finally diagnosed. Membership in a less commonly affected ethnic group may delay or hinder the correct diagnosis.

In general, symptoms involving one or more of the following broad groups should lead to suspicion of FMF: Unexplained recurrent fevers, polyserositis, skin rash, and/or joint pain; abnormal blood studies (see below); and renal or other disease associated with amyloidosis. A family history of FMF or its symptoms would obviously be an important clue, but the recessive nature of FMF means there usually is no family history. The diagnosis may be confirmed when a person with unexplained fever and pain responds to treatment with colchicine since colchicine is not known to have a beneficial effect on any other condition similar to FMF. Abnormal results on a blood test typically include leukocytosis (elevated number of neutrophils in the blood), an increased erythrocyte sedimentation rate (rate at which red blood cells form a sediment in a blood sample), and increased levels of proteins associated with inflammation (called acute phase reactants) such as SAA.

Direct analysis of the MEFV gene for FMF mutations is the only method to be certain of the diagnosis. However, it is not yet possible to detect all MEFV gene mutations that might cause FMF. Thus, if DNA analysis is negative, clinical methods must be relied upon. If both members of a couple were proven to be FMF carriers through **genetic testing**, highly accurate prenatal diagnosis would be available in any subsequent pregnancy.

Similar syndromes of periodic fever and inflammation include familial Hibernian fever and hyperimmunoglobulinemia D syndrome, but both are more rare than FMF.

Treatment and management

Colchicine is a chemical compound that can be used as a medication, and is frequently prescribed for gout. Some

years ago, colchicine was discovered to also be effective in reducing the frequency and severity of attacks in FMF. Treatment for FMF at this point consists of taking colchicine daily. Studies have shown that about 75% of FMF patients achieve complete remission of their symptoms, and about 95% show marked improvement when taking colchicine. Lower effectiveness has been reported, but there is some question about the number of FMF patients who choose not to take their colchicine between attacks when they are feeling well, and thus lose some of the ability to prevent attacks. Compliance with taking colchicine every day may be hampered by its side effects, which include diarrhea, nausea, abdominal bloating, and gas. There is a theoretical risk that colchicine use could damage **chromosomes** in sperms and eggs, or in an embryo during pregnancy, or that it might reduce fertility. However, studies looking at reproduction in men and women who have used colchicine have so far not shown any increased risks. Colchicine is also effective in preventing, delaying, or reversing renal disease associated with amyloidosis.

Other medications may be used as needed to deal with the pain and fever associated with FMF attacks. Dialysis and/or renal transplant might become necessary in someone with advanced kidney disease. Given its genetic nature, there is no cure for FMF, nor is there likely to be in the near future. Any couple that has a child diagnosed with FMF, or anyone with a family history of the condition (especially those in high-risk ethnic groups), should be offered **genetic counseling** to obtain the most up-to-date information on FMF and testing options.

Prognosis

For those individuals who are diagnosed early enough and take colchicine consistently, the prognosis is excellent. Most will have very few, if any, attacks of fever and polyserositis, and will likely not develop serious complications of amyloidosis. The problem of misdiagnosing FMF continues, but education attempts directed at both the public and medical care providers should improve the situation. Future research should provide a better understanding of the inflammation process, focusing on how neutrophils are genetically regulated. That information could then be used to develop treatments for FMF with fewer side effects, and might also assist in developing therapies for other diseases in which abnormal inflammation and immune response are a problem.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. <http://www.nsgc.org/GeneticCounselingYou.asp>.

Scott J. Polzin, MS, CGC

Familial polyposis coli (FPC) *see* **Familial adenomatous polyposis**

Familial somatotrophinoma *see* **Acromegaly**

Familial spastic parapelegia *see* **Hereditary spastic paraplegia**

Fanconi anemia

Definition

Fanconi anemia is an inherited disorder characterized by a severe form of anemia and various other physical malformations. Patients with Fanconi anemia are susceptible to various types of **cancer**.

Description

Fanconi anemia (FA) was first described in 1927 by a Swiss pediatrician named Guido Fanconi. It is a rare, inherited form of *aplastic anemia*. Aplastic anemia is a

KEY TERMS

Androgens—A group of steroid hormones that stimulate the development of male sex organs and male secondary sex characteristics.

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Aplastic anemia—A form of anemia characterized by a greatly decreased formation of red and white blood cells as a result of abnormal bone marrow.

Hematopoetic growth factors—Substances that assist in the formation of blood cells.

Hyperpigmentation—An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

Leukemia—Cancer of the blood forming organs which results in an overproduction of white blood cells.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

Red blood cells—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

White blood cell—A cell in the blood that helps fight infections.

life-threatening condition in which a person is unable to produce adequate amounts of *red blood cells*, *white blood cells*, or *platelets*. Red blood cells serve to carry oxygen to all areas of the body. White blood cells help to fight infection and disease. Platelets are responsible for clotting to help to heal wounds and control bleeding. Without adequate amounts of these important blood cells, patients affected with aplastic anemia are easily fatigued and susceptible to infections. Most cases of aplastic anemia develop throughout the course of a person's lifetime. However, in FA, the aplastic anemia is inherited, or present from birth.

FA is also associated with various other findings. These include short stature, skeletal abnormalities, kidney problems, and heart defects. Additionally, people with FA experience a high incidence of leukemia and an increased incidence of other types of cancer.

The **chromosomes** in the cells of FA patients break and rearrange easily. Chromosomes are the information manuals of our cells. Genes are arranged on chromosomes in a linear fashion, like beads are arranged on a string. Genes tell our cells how to make proteins. These proteins perform many vital functions in the body. When chromosomes break, genes are disrupted and they do not function correctly. This leads to abnormal proteins and various health problems. The chromosome breakage in FA can be seen in the laboratory and is used to diagnose the disorder.

Genetic profile

It has been determined that there are at least eight different genes associated with FA. A change in any one of these genes causes the disorder. As of 2001, the proteins made by these genes are not yet known and their role in FA is not yet understood.

For someone to be affected with FA, each of their parents must have a defect in the same **gene**. Parents that carry the defective gene do not show symptoms of FA because they have a corresponding gene on the other chromosome that produces an adequate amount of protein. Thus, they often do not know they are carriers until they have an affected child. If both parents carry the same defective gene, each pregnancy has a 25% chance of inheriting both abnormal genes and being affected with FA. Likewise, each pregnancy has a 25% chance of inheriting two functional copies of the gene and being unaffected. This leaves a 50% chance that the pregnancy will have one functional gene and one defective gene and will be an unaffected carrier of the disorder. This pattern is known as autosomal recessive **inheritance**.

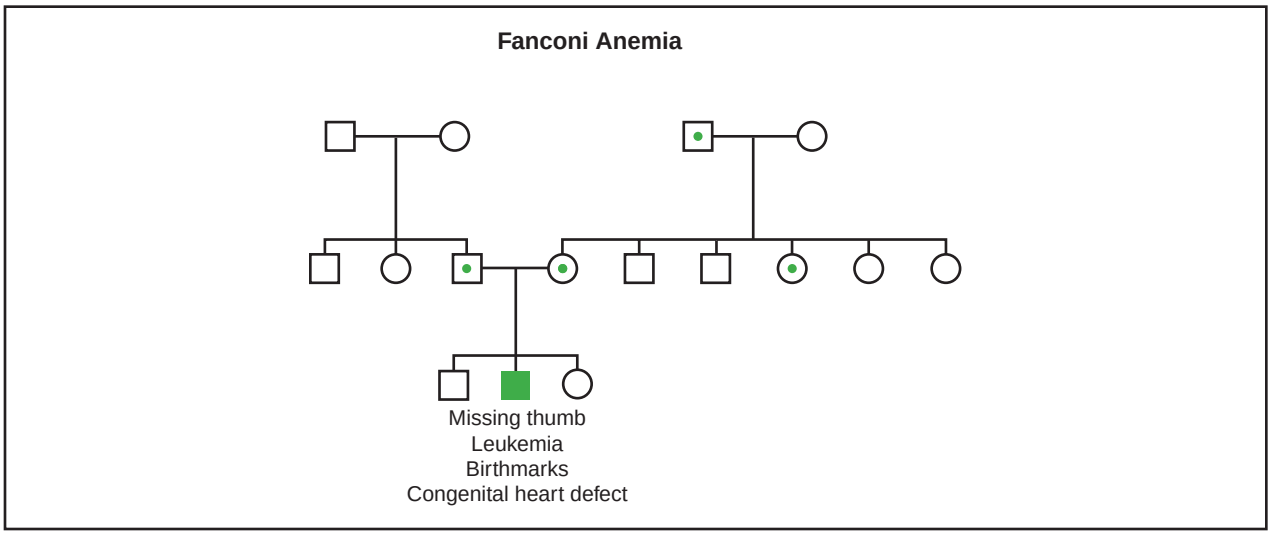
The FA genes are designated by a letter of the alphabet. Defects in the FA-A gene account for approximately 65% of FA cases. Defects in the FA-C gene account for about 15% of FA cases. In the Ashkenazi Jewish population, however, defects in this particular gene are responsible for nearly all cases of FA.

Demographics

FA occurs equally in males and females. The total number of FA patients has not been documented. It has been estimated, however, that between one in 100 and one in 600 people carry one of the defective genes. FA is found in all ethnic groups but is more frequent in the Ashkenazi Jewish population. One in every 89 people in this population carry a mutation in the FA-C gene.

Signs and symptoms

The signs and symptoms of FA generally appear between the ages of three and 12. In rare cases, symptoms



(Gale Group)

do not present until adulthood. These symptoms vary in severity from case-to-case. Even within a family, siblings who are both affected may show very different signs of the disorder.

Aplastic anemia is the first sign of FA in many patients. In some cases, it may be the only sign of the disorder. In aplastic anemia, the bone marrow does not produce an adequate amount of red cells, white cells, or platelets. This can lead to several conditions. Anemia can result due to the deficiency in red blood cells, leading to weakness, fatigue, and a pale appearance. Without enough white blood cells, the patient may be vulnerable to common germs and infections. The deficiency in platelets can cause easy bruising, nosebleeds, and possible internal bleeding.

Ten to fifteen percent of patients with FA develop leukemia, specifically acute myelogenous leukemia (AML). Leukemia is a cancer of the blood system in which abnormal white blood cells grow rapidly in number and suppress the development of healthy blood cells. AML is a particularly aggressive type of leukemia and is difficult to treat successfully. Individuals with FA are very sensitive to the toxic drugs used to fight leukemia, which makes treatment even more difficult.

Among the physical defects associated with FA, short stature is very common. Additionally, an affected child may be born with missing, misshapen, or extra thumbs, or an underdeveloped or missing bone in the arm. Approximately one-fifth of patients with FA exhibit other skeletal abnormalities, such as those of the hip, spine, or rib. About 25% of individuals with FA are born with abnormalities of the kidneys. Some are born with defects of the heart, stomach, esophagus, or intestinal tract. These problems may require immediate surgery at birth.

FA is also associated with hyperpigmentation, or a darkening of the skin, in approximately 65% of patients. This darkening may be present in the form of spots or it may be more diffuse over a larger portion of the body. Additionally, the head or eyes might be smaller than average and some patients may not grow properly. Learning disabilities are thought to be fairly common in FA as well. Hearing loss has been reported in 10% of patients.

As these individuals become older, other problems may result. In males, it is common to see underdeveloped male organs and infertility. Females often have a delay in the start of their menstrual periods and a decrease in fertility. Menopause may occur as early as age 30.

People with FA, especially those over the age of 20, are at a high risk to develop cancerous tumors in the head, neck, intestines, urinary tract, liver, and esophagus. Women are also at an increased risk for cancers of the reproductive tract.

Diagnosis

The most common test for FA is called a chromosome breakage test. White blood cells are isolated from a patient's blood sample and destructive chemicals are added to these cells. The chromosomes are then viewed under a microscope. If the person is not affected with FA, the chromosomes will appear normal. If the person is affected with FA, the chromosomes will be broken and rearranged. Skin cells can be tested in a similar fashion and will often show this chromosome breakage as well.

This particular test can be completed prenatally if a family desires to know whether or not a child is affected before he or she is born. Cells obtained from the mother's placenta or cells floating in the amniotic fluid that surrounds the fetus in the womb can be used to detect chromosome breakage.

For families who have a defect in the FA-C gene, it is possible to look directly at the gene to determine whether or not a defect is present. This can detect those who carry the gene defect as well as those who are affected. Carrier testing is offered routinely to those in the Ashkenazi Jewish population since the frequency of carriers is so high.

Treatment and management

Once the diagnosis of FA has been made, several initial tests should be completed, including liver and kidney function studies, a formal hearing evaluation, a developmental assessment, and an ultrasound examination of the kidneys and urinary system.

People affected with FA should be followed closely by a physician. Their blood cell and platelet counts should be monitored frequently. Symptoms caused by anemia and low platelets, such as bleeding, fatigue, chest pain, and dizziness, can be treated with transfusions as needed. Antibiotics are often given to fight infections. At times, hospitalization may be necessary to adequately tend to these complications. As patients get older, they should be monitored for any signs of solid tumor cancers.

Due to either aplastic anemia or leukemia, many individuals with FA will eventually require a bone marrow transplant. The donor must be carefully matched to the patient. The prognosis for transplant is best for young patients who have an sibling donor with a matching tissue type.

Between 50 and 75% of individuals with FA will respond to androgens. These are artificial male hormones that can stimulate production of one or more types of blood cells. They are most effective in increasing the number of red blood cells but can increase platelets and white cells as well. These drugs prolong the lives of individuals with FA but are not a cure.

As of 2001, various hematopoetic growth factors have been studied in relation to FA. These substances are already present in the body and serve to stimulate the production of blood cells and platelets. Scientists have developed a way to manufacture these substances. They have been given to patients with FA and show promise in increasing the counts of blood cells and platelets.

Prognosis

FA is an unpredictable illness. The average life expectancy for an affected individual is 22 years, but any one individual can have a lifespan that is quite different from this average. Research discoveries have led to life-extending treatments and improved bone marrow transplant outcome. However, as patients live longer, they become at an increased risk to develop other types of tumors.

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Fanconi Anemia Research Fund. 1801 Willamette St., Suite 200, Eugene, OR 97401-4030. (800) 828-4891. <http://www.fanconi.org>.

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Mary E. Freivogel, MS

Fanconi-Bickel syndrome

Definition

Fanconi-Bickel syndrome (FBS) is a rare inherited disorder of carbohydrate metabolism caused by mutations in the **gene** known as GLUT2.

Description

Also known as glycogen storage disease type XI, the disease was first described by scientists G. Fanconi and Horst Bickel in 1949. Since then, only a few dozen cases of FBS have been studied, most in the United States, Europe, and Japan.

Onset of FBS is within the first year of life, with the overt symptom being a failure to thrive. At age two, an

enlarged liver and kidneys are present and the child has rickets. The incidence of FBS has not been determined but it is believed to occur in less than one in one million births.

Genetic profile

FBS is believed to be an autosomal recessive disorder. This means that an individual with FBS would have to inherit an abnormal copy of the gene from both parents in order to show symptoms of FBS. People with only one abnormal gene are carriers and do not have the disorder. When both parents have the abnormal gene, there is a 25% chance with each birth that their child will inherit both abnormal genes and have the disease. There is a 50% chance each birth that the child will inherit one abnormal gene and become a carrier of the disorder but not have the disease itself. There is a 25% chance each child will inherit neither abnormal gene and not have the disease nor be a carrier. The specific genetic defect of FBS has not been identified.

Demographics

Since there is so little research on Fanconi-Bickel syndrome, no clear pattern of demographics has been established. However, the disorder is known to affect both males and females. One common thread in some of the cases that have been studied has been consanguinity, meaning that FBS is found in the children of two persons of the same blood relation. In several of these cases the consanguinity is between two first cousins.

Signs and symptoms

In a 1987 study by researchers at the Research Institute for Child Nutrition in Dortmund, Germany, nine cases of Fanconi-Bickel syndrome were compared for clinical symptoms, behavior symptoms, and physical appearance. The initial symptoms reported were fever, vomiting, growth failure, and rickets between the ages of three and ten months. Later, these same patients showed signs of dwarfism, a protruding abdomen, enlarged liver, moon-shaped face, and abnormal fat deposits around the shoulders and abdomen. Also, cutting of teeth and puberty were delayed. Complications present included fractures and pancreatitis (an enlarged pancreas). Later in life, rickets and osteoporosis were constant features.

The German study, whose researchers included H. Bickel, co-discoverer of the syndrome, also used ultrasound to determine increased kidney size and growth in relation to body height. The most prominent finding was glucosuria (glucose, or sugar, in the urine). Polyuria (increased urination) was also a constant finding. The study noted that liver size was normal or slightly increased at birth in all nine cases but became greatly enlarged during infancy. The liver size and glycogen (a glucose storage molecule) content were reduced when the patients were placed on an antiketogenic (high carbohydrate) diet.

Other laboratory findings included fasting hypoglycemia (low levels of sugar in the blood), ketonuria (high levels of ketones in the urine), high hypercholesterolemia (high cholesterol), **hypophosphatemia** (high phosphate levels in the blood), and high levels of amino acids and protein in the urine. In a 1995 study at Children's Hospital in Philadelphia of an eight-year-old with Fanconi-Bickel syndrome, doctors reported additional symptoms of overworked kidneys, very small amounts of albumin (a class of water soluble proteins) in the urine, and an increase in the number of cells in the inner part of the kidney that filters blood.

Diagnosis

Fanconi-Bickel syndrome can usually be identified in patients by neonatal screening for galactose, a type of sugar. Patients with FBS are intolerant to galactose. Other diagnostic factors include an impaired glucose tolerance test, x ray to determine the pattern of rickets, urine tests to measure levels of glycose, phosphates, amino acids, and bicarbonate, and a liver biopsy to detect abnormal galactose oxidation.

KEY TERMS

Carbohydrate—Any of various natural compounds of carbon, hydrogen, and oxygen (as in sugars and starches) that are burned by the body for energy.

Diabetes mellitus—The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

Hyperlordosis—An exaggerated curve in the lower (lumbar) portion of the back.

Osteoporosis—Loss of bone density that can increase the risk of fractures.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Pancreatitis—Inflammation of the pancreas.

Rickets—A childhood disease caused by vitamin D deficiency, resulting in soft and malformed bones.

Treatment and management

There is no effective treatment for Fanconi-Bickel syndrome. However, some of the symptoms can be treated with adequate supplementation of water, electrolytes, and vitamin D, restriction of galactose, and a diabetes mellitus-like diet (low sugar and low carbohydrate) presented in frequent small meals. These treatments can improve growth and give the patient a general sense of well-being.

Prognosis

The long-term prognosis has not been determined. It may depend on the severity of symptoms and early diagnosis and treatment of symptoms. The first person diagnosed with the disorder in 1949 was a four-year-old Swiss boy with consanguineous parents. At six months, the boy had excessive thirst, constipation, and was not thriving. He was treated with vitamin D and calcium supplements. At about age four, the boy had short stature, a protruding abdomen, an enlarged liver, facial obesity, osteopenia, and hyperlordosis. At age 12, the boy was found to be resistant to glycogen. In 1997 at age 52, the patient, without any treatment other than vitamin D and calcium supplements, was of short stature (4 ft 8 in or 140 cm tall), weighed about 95 lbs (43 kg), had a moderately protruding abdomen, and a smaller than normal liver. Other than arthritis, he had no medical complaints. However, other people diagnosed as children with FBS had much shorter life spans. Long-term follow-up studies of nine persons with FBS showed severely retarded growth, partly compensated for by late onset of puberty.

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ORGANIZATIONS

American Association of Kidney Patients. 100 S. Ashley Dr., Suite 280, Tampa, FL 33602. (800) 749-2257. <http://www.aakp.org>.

National Kidney Foundation. 30 East 33rd St., New York, NY 10016. (800) 622-9010. <http://www.kidney.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Ken R. Wells

Fatty aldehyde dehydrogenase deficiency (FALDH10 deficiency) *see* Sjögren Larsson syndrome

Feingold syndrome *see* Oculo-digito-esophago-duodenal syndrome

Fetal alcohol syndrome

Definition

Fetal alcohol syndrome (FAS) is a pattern of birth defects, learning, and behavioral problems affecting individuals whose mothers consumed alcohol during pregnancy.

Description

FAS is the most common preventable cause of mental retardation. This condition was first recognized and reported in the medical literature in 1968 in France and in 1973 in the United States. Alcohol is a **teratogen**, the term used for any drug, chemical, maternal disease or other environmental exposure that can cause birth defects or functional impairment in a developing fetus. Some features may be present at birth including low birth weight, prematurity, and microcephaly. Characteristic facial features may be present at birth, or may become more obvious over time. Signs of brain damage include delays in development, behavioral abnormalities, and mental retardation, but affected individuals exhibit a wide range of abilities and disabilities. It has only been since 1991 that the long-term outcome of FAS has been known. Learning, behavioral, and emotional problems are common in adolescents and adults with FAS. Fetal alcohol effect (FAE), a term no longer favored, is sometimes used to describe individuals with some, but not all, of the features of FAS. In 1996, the Institute of Medicine suggested a five-level system to describe the birth defects, learning and behavioral difficulties in offspring of women who drank alcohol during pregnancy. This system contains criteria including confirmation of maternal alcohol exposure, characteristic facial features, growth problems, learning and behavioral problems, and birth

defects known to be associated with prenatal alcohol exposure.

The incidence of FAS varies among different populations studied, and ranges from approximately one in 200 to one in 2000 at birth. However, a recent study reported in 1997, utilizing the Institute of Medicine criteria, estimated the prevalence in Seattle, Washington from 1975–1981 at nearly one in 100 live births. Avoiding alcohol during pregnancy, including the earliest weeks of the pregnancy, can prevent FAS. There is no amount of alcohol use during pregnancy that has been proven to be completely safe.

Genetic profile

FAS is not a genetic or inherited disorder. It is a pattern of birth defects, learning, and behavioral problems that are the result of maternal alcohol use during the pregnancy. The alcohol freely crosses the placenta and causes damage to the developing embryo or fetus. Alcohol use by the father cannot cause FAS. If a woman who has FAS drinks alcohol during pregnancy, then she may also have a child with FAS. Not all individuals from alcohol exposed pregnancies have obvious signs or symptoms of FAS; individuals of different genetic backgrounds may be more or less susceptible to the damage that alcohol can cause. The dose of alcohol, the time during pregnancy that alcohol is used, and the pattern of alcohol use all contribute to the different signs and symptoms that are found.

Demographics

There is no racial or ethnic predilection for FAS. Individuals from different genetic backgrounds exposed to similar amounts of alcohol during pregnancy may exhibit different signs or symptoms of FAS. Several studies have estimated that 25-45% of chronic alcoholic women will give birth to a child with FAS if they continue to drink during pregnancy. The risk of FAS appears to increase as a chronic alcoholic woman progresses in her childbearing years and continues to drink. That is, a child with FAS will often be one of the last born to a chronic alcoholic woman, although older siblings may exhibit milder features of FAS. Binge drinking, defined as sporadic use of five or more standard alcoholic drinks per occasion, and "moderate" daily drinking (two to four 12 oz bottles of beer, eight to 16 ounces of wine, two to four ounces of liquor) can also result in offspring with features of FAS.

Signs and symptoms

Classic features of FAS include short stature, low birthweight and poor weight gain, microcephaly, and a characteristic pattern of facial features. These facial features in infants and children may include small eye openings (measured from inner corner to outer corner), epicanthal folds (folds of tissue at the inner corner of the eye), small or short nose, low or flat nasal bridge, smooth or poorly developed philtrum (the area of the upper lip above the colored part of the lip and below the nose), thin upper lip, and small chin. Some of these features are nonspecific, meaning they can occur in other conditions, or be appropriate for age, racial, or family background. Other major and minor birth defects that have been reported include cleft palate, **congenital heart defects**, strabismus, hearing loss, defects of the spine and joints, alteration of the hand creases and small fingernails and toenails. Since FAS was first described in infants and children, the diagnosis is sometimes more difficult to recognize in older adolescents and adults. Short stature and microcephaly remain common features, but weight may normalize, and the individual may actually become overweight for his/her height. The chin and nose grow proportionately more than the middle part of the face and dental crowding may become a problem. The small eye openings and the appearance of the upper lip and philtrum may continue to be characteristic. Pubertal changes typically occur at the normal time.

KEY TERMS

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Congenital—Refers to a disorder which is present at birth.

IQ—Abbreviation for Intelligence Quotient. Compares an individual's mental age to his/her true or chronological age and multiplies that ratio by 100.

Microcephaly—An abnormally small head.

Miscarriage—Spontaneous pregnancy loss.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Strabismus—An improper muscle balance of the ocular musles resulting in crossed or divergent eyes.

Teratogen—Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

Newborns with FAS may have difficulties with feeding due to sucking difficulties, have irregular sleep-wake cycles, decreased or increased muscle tone, or seizures or tremors. Delays in achieving developmental milestones such as rolling over, crawling, walking, and talking may become apparent in infancy. Behavior and learning difficulties typical in the preschool or early school years include poor attention span, hyperactivity, poor motor skills, and slow language development. Attention deficit-hyperactivity disorder is a common associated diagnosis. Learning disabilities or mental retardation may be diagnosed during this time. Arithmetic is often the most difficult subject for a child with FAS. During middle school and high school years the behavioral difficulties and learning difficulties can be significant. Memory problems, poor judgment, difficulties with daily living skills, difficulties with abstract reasoning skills, and poor social skills are often apparent by this time. It is important to note that animal and human studies have shown that neurologic and behavioral abnormalities can be present without characteristic facial features. These individuals may not be identified as having FAS, but may fulfill criteria for alcohol related diagnoses, as set forth by the Institute of Medicine.

In 1991, Streissguth and others reported some of the first long-term follow-up studies of adolescents and adults with FAS. In the approximately 60 individuals they studied, the average IQ was 68, with 70 being the lower limit of the normal range. However, the range of IQ was quite large, as low as 20 (severely retarded) to as high as 105 (normal). The average achievement levels for reading, spelling, and arithmetic were fourth grade, third grade and second grade, respectively. The Vineland Adaptive Behavior Scale was used to measure adaptive functioning in these individuals. The composite score for this group showed functioning at the level of a seven-year-old. Daily living skills were at a level of nine years, and social skills were at the level of a six-year-old.

In 1996, Streissguth and others published further data regarding the disabilities in children, adolescents, and adults with FAS. Secondary disabilities, that is, those disabilities not present at birth and that might be preventable with proper diagnosis, treatment, and intervention, were described. These secondary disabilities include: mental health problems; disrupted school experiences; trouble with the law; incarceration for mental health problems, drug abuse, or a crime; inappropriate sexual behavior; alcohol and drug abuse; problems with employment; dependent living; and difficulties parenting their own children. In that study, only seven out of 90 adults were living and working independently and successfully. In addition to the studies by Streissguth, several other authors in different countries have now reported on long term outcome of individuals diagnosed with FAS. In general, the neurologic, behavioral, and emotional disorders become the most problematic for the individuals. The physical features change over time, sometimes making the correct diagnosis more difficult in older individuals, without old photographs and other historical data to review. Mental health problems including attention deficit, **depression**, panic attacks, psychosis, and suicide threats and attempts were present in over 90% of the individuals studied by Streissguth. A 1996 study in Germany reported more than 70% of the adolescents they studied had persistent and severe developmental disabilities and many had psychiatric disorders, the most common of which were emotional disorders, repetitive habits, speech disorders, and hyperactivity disorders.

Diagnosis

FAS is a clinical diagnosis, which means that there is no blood, x ray, or psychological test that can be performed to confirm the suspected diagnosis. The diagnosis is made based on the history of maternal alcohol use, and detailed physical examination for the characteristic major and minor birth defects and characteristic facial features. It is often helpful to examine siblings and parents of an individual suspected of having FAS, either in person or by photographs, to determine whether findings on the examination might be familial, of if other siblings may also be affected. Sometimes, genetic tests are performed to rule out other conditions that may present with developmental delay or birth defects. Individuals with developmental delay, birth defects, or other unusual features are often referred to a clinical geneticist, developmental pediatrician, or neurologist for evaluation and diagnosis of FAS. Psychoeducational testing to determine IQ and/or the presence of learning disabilities may also be part of the evaluation process.

Treatment and management

There is no treatment for FAS that will reverse or change the physical features or brain damage associated with maternal alcohol use during the pregnancy. Most of the birth defects associated with prenatal alcohol exposure are correctable with surgery. Children should have psychoeducational evaluation to help plan appropriate educational interventions. Common associated diagnoses such as attention deficit-hyperactivity disorder, depression, or anxiety should be recognized and treated appropriately. The disabilities that present during childhood persist into adult life. However, some of the secondary disabilities mentioned above may be avoided or lessened by early and correct diagnosis, better understanding of

the life-long complications of FAS, and intervention. Streissguth has described a model in which an individual affected by FAS has one or more advocates to help provide guidance, structure, and support as the individual seeks to become independent, successful in school or employment, and develop satisfying social relationships.

Prognosis

The prognosis for FAS depends on the severity of birth defects and the brain damage present at birth. Miscarriage, stillbirth, or death in the first few weeks of life may occur in very severe cases. Major birth defects associated with FAS are usually treatable with surgery. Some of the factors that have been found to reduce the risk of secondary disabilities in FAS individuals include diagnosis before the age of six years, stable and nurturing home environments, never having experienced personal violence, and referral and eligibility for disability services. The long-term data helps in understanding the difficulties that individuals with FAS encounter throughout their lifetime and can help families, caregivers, and professionals provide the care, supervision, education, and treatment geared toward their special needs.

Prevention of FAS is the key. Prevention efforts must include public education efforts aimed at the entire population, not just women of child-bearing age, appropriate treatment for women with high-risk drinking habits, and increased recognition and knowledge about FAS by professionals, parents, and caregivers.

Resources

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Streissguth, Ann Pytkowicz, et al. "Fetal Alcohol Syndrome in Adolescents and Adults." *JAMA* 265 (April 1991): 1961-1967.

ORGANIZATIONS

Arc's Fetal Alcohol Syndrome Resource Guide. The Arc's Publication Desk, 3300 Pleasant Valley Lane, Suite C, Arlington, TX 76015. (888) 368-8009. <http://www.thearc.org/misc/faslist.html>.

Fetal Alcohol Syndrome Family Resource Institute. PO Box 2525, Lynnwood, WA 98036. (253) 531-2878 or (800) 999-3429. <http://www.fetalalcoholsyndrome.org>.

Institute of Medicine. National Academy Press, Washington, DC <http://www.come-over.to/FAS/IOMsummary.htm>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

Nofas. 216 G St. NE, Washington, DC 20002. (202) 785-4585. <http://www.nofas.org>.

Laurie Heron Seaver, MD

Fetal facies syndrome *see* **Robinow syndrome**

FG syndrome

Definition

FG syndrome (FGS) is a genetic disorder characterized by mental retardation, low muscle tone (hypotonia), large head, constipation, and anal abnormalities.

Description

FGS refers to a rare genetic condition that has a variety of physical and mental symptoms. Most individuals affected by FGS have symptoms including mental retardation, low muscle tone, brain abnormalities (partial agenesis of the corpus callosum), seizures, large head, characteristic facial features, large intestinal and anal abnormalities, constipation, short stature, joints that tend to stay in one place (fixed), broad big toes, and light and

KEY TERMS

Heterogeneous—A set of symptoms or a disorder caused by several different gene mutations.

Imperforate anus—Also known as anal atresia. A birth defect in which the opening of the anus is absent or obstructed.

Variable penetrance—A term describing the way in which the same mutated gene can cause symptoms of different severity and type within the same family.

dark skin streaking. The syndrome was first described by Opitz and Kaveggia in 1974 based on physical findings and family history. All of these features appear to be caused by mutated or changed genes on the X chromosome. Although the full effect of the mutation or change in the **gene** is not fully understood, the mutations are believed to interrupt the genes' normal functions in the brain, digestive tract, and muscle tissue.

Other names for FG syndrome include Opitz-Kaveggia Syndrome and Keller syndrome.

Genetic profile

FGS is caused by mutations on the long arm of the X-chromosome. Studies in 1998 and 2000 found that individuals affected by FGS can have a mutation on the X-chromosome in two different locations on the long arm (q) of the X-chromosome: Xq12-Xq21 [called FGS1] and Xq28 [called FGS2]. When a set of symptoms are caused by gene mutations at different locations, the disorder is called heterogeneous. Although a **gene mutation** causing FGS can appear in an individual for the first time and is not found in the affected individual's parents, most cases of FGS are inherited.

Since both possible gene mutations are found on the X chromosome, FGS is inherited in an X-linked recessive pattern. Every individual has approximately 30,000–35,000 genes that tell their bodies how to form and function. Each gene is present in pairs, since one is inherited from their mother and one is inherited from their father. Females have two X **chromosomes**, while males have a single X chromosome and Y chromosome. In other words, females receive two copies of the genetic information stored on the X chromosome. When a female inherits the gene for an X-linked recessive condition, she is known as a "carrier." She usually has no problems related to that condition, because the gene on her other X chromosome continues to function properly and "masks" the abnormal gene. However, males only inherit one copy of the information stored on the X chromosome. When a male inherits the gene for an X-linked recessive condition, he will experience the symptoms associated with that condition. The mutated or changed genes which cause FGS are located on the X chromosome and thus the full-blown disorder primarily affects males carrying the mutated or changed gene on their one X chromosome. When a condition is X-linked, the gene for the condition travels through the family on the X chromosome. In X-linked genetic conditions, the risk for a carrier female to have an affected son is 50%, while the risk to have a carrier daughter is also 50%. An affected male has a 100% chance of having carrier daughters and no chance to have an affected son.

Individuals inheriting the same mutated gene in the same family can have very different symptoms. For example, approximately 38% of individuals affected by FGS have anal anomalies, like a missing anal opening (imperforate anus), while mental retardation is present in 97% of individuals affected by FGS. The difference in physical findings within the same family is known as variable penetrance or intrafamilial variability.

Demographics

FG syndrome can appear in any ethnic population. FGS has been described in individuals of Japanese, American, European, African, and other ethnic background. FGS is not believed to be more common in one specific population.

Signs and symptoms

Individuals affected by FG syndrome (can be affected by a variety of symptoms. Most affected individuals have signs of FGS such as mental retardation, low muscle tone and physical development, seizures, large heads, big foreheads, a front cowlick of hair, wide-spaced eyes, extra eye folds (short, palpebral fissures), constipation, and an outgoing, talkative personality. Other fairly common signs of FGS include anal abnormalities (imperforate anus), brain abnormalities (partial agenesis of the corpus callosum, hearing impairments, broad thumbs and big toes, small ears, fine/thinning hair, fused fingers, minor back bone abnormalities, **cleft lip and palate**, heart defects, and fetal fingertip pads.

Diagnosis

Diagnosis of FGS is usually made from physical examination by a medical geneticist. The physical examination looks for the combined characteristic features, low muscle tone, mental retardation, etc., of FGS.

Although mutations in specific genes that cause FGS have been found, molecular **genetic testing** (prenatal or diagnostic) is not available in 2001.

Treatment and management

FG syndrome does not have a specific therapy that removes, cures, or fixes all signs of the disorder.

Management and treatment for FGS mainly focuses on the treatment of specific symptoms. More specifically, individuals with incompletely formed anal openings and serious heart defects would need surgery to try to correct the problems. Individuals affected by FGS who have mental retardation benefit from special school and early intervention programs.

Prognosis

The prognosis of an individual affected by FGS depends on the severity of the symptoms by which they are affected. For example, approximately one-third of individuals affected by FGS will die before two years of age due to the severity of heart defects and anal abnormalities.

Most individuals affected by FGS who do not have severe physical problems, such as serious heart defects and anal abnormalities, are still affected by mental retardation. Individuals affected by FGS who have mental retardation benefit from special schools and early intervention programs.

Resources

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Trainer, Marilyn, and Helen Featherstone. *Differences in Common: Straight Talk on Mental Retardation, Down Syndrome, and Your Life.* Bethesda, MD: Woodbine House, 1991.

PERIODICALS

FG Syndrome Family Alliance Print Newsletter FG Syndrome Family Alliance, subscribe by sending email to: FGSNewsl@aol.com

ORGANIZATIONS

Arc (a National Organization on Mental Retardation). 1010 Wayne Ave., Suite 650, Silver Spring, MD 20910. (800) 433-5255. <http://www.thearclink.org>.

WEBSITES

The Family Village. <http://www.familyvillage.wisc.edu>.

FG Syndrome Family Alliance. FG Syndrome Homepage. <http://www.geocities.com/HotSprings/Spa/3687/>.

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Dawn A. Jacob, MS

Fibroblast growth factor receptor mutations

Definition

Fibroblast growth factor receptors (FGFRs) are a family of proteins specialized in growth inhibition. Mutations in these molecules lead to various **genetic disorders** involving short stature and/or premature fusion of the bones of the skull. There are at least four known FGFRs (FGFR1, FGFR2, FGFR3, FGFR4).

Description

As a group, FGFRs are very similar to each other in their structure and function. All are transmembrane proteins composed of three distinct parts. A binding site on the exterior of the cell membrane, an active site on the interior of the cell membrane, and a connecting section spanning the cell membrane and joining the inner and outer components.

Fibroblast growth factors (FGFs) attach to the binding site of extracellular portion of the FGFR protein. There are at least 17 known FGFs that bind and interact with FGFRs. Two FGFs must first bind with each other and, as a pair, are able to fit into the FGFR binding site forming an FGF/FGFR complex. FGF pairing and FGF/FGFR binding is non-specific, with any two FGFs coupling and binding any FGFR.

When the binding site is empty and no FGF is bound, the FGFR is inactive and cellular growth continues unchecked. When an FGF pair binds, the FGF/FGFR complex sends a signal that travels the length of the FGFR protein, resulting in the stimulation of the active site on the inside of the cell membrane.

The active site of the FGFR stimulates molecules within the cell through the biochemical process of phosphorylation. Each activated molecule goes on to affect another molecule, thereby propagating the original signal and, much like the domino effect, a cascade of events is triggered. The process continues, molecule by molecule, until the signal reaches the nucleus of the cell, ultimately resulting in the inhibition of cell growth.

Although highly recognized in the process of growth restriction, FGFRs are also thought to be involved in a

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance, a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Genome—A term used to describe a complete representation of all of the genes in a species.

Phosphorylation—The addition of phosphoric acid to another compound.

Transmembrane—Anything that spans the width of a membrane.

wide variety of biological processes including migration of cells during embryo development, blood vessel growth, wound healing, cell death, and **cancer**.

Genes

A different **gene** codes for each of the four types of FGFR proteins (Table 1). Genes are the genetic material passed down from generation to generation that tell a person's body how to work and how to grow. Genes are packaged into **chromosomes**, with hundreds of genes on each chromosome. Individual cells contain 46 chromosomes, which may be matched into 23 pairs. One of each pair is inherited from the egg of the mother and one of each pair is inherited from the sperm of the father.

A mutation, meaning a change in an FGFR gene, also changes the structure of the FGFR protein, which then affects the protein's function. Most FGFR gene mutations are thought to cause the protein receptors to become overly active. These defective receptors continuously start the activation cascade independent of FGF binding. This causes a strong slowing-down effect on growth, which is readily observed in the symptoms of affected individuals. Common features of the disease include abnormalities of the limbs, skin, head, and face.

TABLE 1

FGFR Genes

Gene	Chromosome	Protein product
FGFR1	8p11	FGFR1
FGFR2	10q26	FGFR2
FGFR3	4p16	FGFR3
FGFR4	5q35	FGFR4

Inheritance

Approximately ten genetic disorders have been linked to abnormal FGFRs. All FGFR-related syndromes are autosomal dominant. That is, although individuals inherit two copies of each gene FGFR gene, only one copy must be mutated for a person to be affected with a disorder. Some individuals with an FGFR-related disorder have a parent affected by the same disease, in which case the disease is said to be familial. Other individuals are the first person in their family to be affected. These cases are considered sporadic, meaning they arose from a new mutation in the affected person's **DNA**.

Whether familial or sporadic, all affected individuals have a 50% chance of passing on the disease to a child in any future pregnancy. The overall risk for a pregnancy can change if an affected person has a child with an individual affected by the same disease.

Prenatal testing

Prenatal testing is available for all of the FGFR-associated syndromes. Some cases are diagnosed based on clinical presentation, while others are diagnosed by DNA mutation analysis. Chorionic villus sampling (CVS) or **amniocentesis** may be used when there is a known familial mutation. If there is no family history of FGFR-related disease, but prenatal examination by ultrasound gives rise to concern, prognosis and diagnosis are traditionally based on clinical findings after birth.

Disease causing mutations

Syndromes involving FGFR gene mutations fall into two categories. The first category includes four disorders of short stature, all caused by mutations in the FGFR3 gene. The second category includes six syndromes involving skull malformations (**craniosynostosis**), all caused by mutations in the FGFR1, FGFR2, or FGFR3

TABLE 2

FGFR-related dwarfism syndromes

Syndrome*	Incidence	Gene	Common mutations[1]
Achondroplasia (ACH)	1/15,00–1/40,000	FGFR3	Gly380Arg
Hypochondroplaisa (HCH)	Unknown	FGFR3	Asn540Lys
Thanatophoric dysplasia Type I (TD1)	1/60,000 (TD1 and TD2)	FGFR3	Arg248Cys
Thanatophoric dysplasia type II (TD2)	See above	FGFR3	Lys650Glu
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	3 reported cases	FGFR3	Lys650Met

*Please see the entry of the specific disease for further information and an exact description of the disorder.
[1]This represents common mutations and is not a complete list of mutations.

genes. As of 2001, there have been no disease-causing mutations reported in the FGFR4 gene.

Dwarfism

FGFR-related dwarfism disorders are all due to abnormal FGFR3 function (Table 2). Mutations in the FGFR3 gene are among the most common mutations in the human genome.

Achondroplasia was the first disease associated with FGFRs. It is the most common form of inherited disproportionate short stature with an incidence of one in 15,000 to one in 40,000 live births. Over 80% of cases of achondroplasia are sporadic, with a strong link to advanced paternal age.

Achondroplasia is characterized by abnormal bone growth that results in short stature with disproportionately short arms and legs, a large head, and characteristic facial features. Intelligence and life span are usually normal, although there is an increased risk of death in infancy from compression of the spinal cord and/or upper airway obstruction.

Hypochondroplasia is a form of short-limbed dwarfism also caused by a mutation in the FGFR3 gene. Although it appears clinically as a mild form of dwarfism, hypochondroplasia is caused by unique mutations in the FGFR3 gene, different than those that cause achondroplasia.

Thanatophoric dysplasia Types I and II and severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) dysplasia are the most severe forms of FGFR-related dwarfism. Both types of **thanatophoric dysplasia** are fatal with death occurring before birth or during early infancy. As of 2001 there have been only three reported cases of SADDAN dysplasia. Although it is much like thanatophoric dysplasia in its presentation, affected individuals survive past infancy. Affected individuals are severely affected both mentally and physically. Both SADDAN dysplasia and thanatophoric dysplasiaa Types I and II have their own distinct FGFR3 gene mutations.

Craniosynostosis

Craniosynostosis is the hallmark feature of the second subset of disorders caused by FGFR gene mutations (Table 3). Craniosynostosis is the premature fusion of some or all of the bones of the skull. During normal development the bones of the skull do not completely fuse until the first to second year of life. This allows for passage through the narrow birth canal at delivery and for maximum brain growth during early developmental years.

There are over 150 genetic disorders that involve craniosynostosis that are not related to FGFR mutations. The collective incidence of all forms of craniosynostosis is 1/2000–1/2500 live births.

As of 2001, there are six craniosynotosis syndromes thought to be FGFR-related. All six display some form of craniosynostosis, distinctive facial features, and hand and foot deformations. Syndromes range from severe (neonatal death) to mild (no clinical manifestations). The characteristic facial features observed include underdevelopment of the midface, protruding eyes, down-slanting eyes, small beaked nose, protruding jaw (prognathism), and eyes that are unusually far apart (hypertelorism). Hand and foot anomalies are distinct for each syndrome and are sometimes used to distinguish between the disorders.

Future

Although the FGFR-related syndromes have been well-characterized, scientists continue to face some puzzling questions. It has been observed that identical FGFR gene mutations may result in two or more clinically distinct disorders, meaning with different symptoms. For example, a single mutation in the FGFR1 gene has been shown to result in **Pfeiffer syndrome**. The same mutation in the FGFR2 gene leads to **Apert syndrome**, while

TABLE 3

FGFR-related craniosynostosis syndromes

Syndrome*	Incidence	Gene	Common Mutations&
Muenke syndrome	Unknown	FGFR3	Pro250Arg
Crouzon syndrome	1.6/100,000	FGFR2	25 mutations
Crouzon with Acanthosis Nigricans	Unknown	FGFR3	Ala391Glu
Jackson-Wiess syndrome	Unknown	FGFR2	Cys342Arg, Ala344Gly
Apert syndrome	1/100,000	FGFR2	Pro250Arg, Ser252Trp
Pfeiffer types 1–3	1/100,000 (collective)	FGFR1, FGFR2	Pro250Arg
Beare-Stevenson cutis gyrata	<10 cases reported	FGFR2	Ser372Cys, Tyr375Cys

*Please see the entry of the specific disease for further information and an exact description of the disorder.
This represents common mutations and is not a complete list of mutations.

the equivalent mutation in the FGFR3 gene produces Muenke craniosynostosis. Likewise, a single mutation in the FGFR2 gene may lead to any of the Crouzon, Pfeiffer, or Jackson-Weiss syndromes. The mechanism by which a particular mutation may lead to multiple different genetic disorders is not clearly understood.

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Fifth digit syndrome *see* **Coffin-Siris syndrome**

Focal dermal hypoplasia (DHOF) *see* **Goltz syndrome**

Fragile site (FRAXE) *see* **Fragile X syndrome**

Fragile site mental retardation 1 (FMR1) *see* **Fragile X syndrome**

Fragile X syndrome

Definition

Fragile X syndrome is the most common form of inherited mental retardation. Individuals with this condition have developmental delay, variable levels of mental retardation, and behavioral and emotional difficulties. They may also have characteristic physical traits. Generally, males are affected with moderate mental retardation and females with mild mental retardation.

Description

Fragile X syndrome is also known as Martin-Bell syndrome, Marker X syndrome, and FRAXA syndrome. It is the most common form of inherited mental retardation. Fragile X syndrome is caused by a mutation in the FMR-1 **gene**, located on the X chromosome. The role of the gene is unclear, but it is probably important in early development.

Genetic profile

In order to understand fragile X syndrome it is important to understand how human genes and **chromosomes** influence this condition. Normally, each cell in the body contains 46 (23 pairs of) chromosomes. These chromosomes consist of genetic material (**DNA**) needed for the production of proteins, which lead to growth, development, and physical/intellectual characteristics. The first 22 pairs of chromosomes are the same in males and females. The remaining two chromosomes are called

the sex chromosomes (X and Y). The sex chromosomes determine whether a person is male or female. Males have only one X chromosome, which is inherited from the mother at conception, and they receive a Y chromosome from the father. Females inherit two X chromosomes, one from each parent. Fragile X syndrome is caused by a mutation in a gene called FMR-1. This gene is located on the X chromosome. The FMR-1 gene is thought to play an important role in the development of the brain, but the exact way that the gene acts in the body is not fully understood.

The mutation involves a short sequence of DNA in the FMR-1 gene. This sequence is designated CGG. Normally, the CGG sequence is repeated between six and 54 times. People who have repeats in this range do not have fragile X syndrome and are not at increased risk to have children with fragile X syndrome. Those affected by fragile X syndrome have expanded CGG repeats (over 200) in the first exon of the FMR1 gene (the full mutation).

For reasons not fully understood, the CGG sequence in the FMR-1 gene can expand to contain between 54 and 230 repeats. This stage of expansion is called a premutation. People who carry a premutation do not usually have symptoms of fragile X syndrome; although there have been reports of individuals with a premutation and subtle intellectual or behavioral symptoms. Individuals who carry a fragile X premutation are at risk to have children or grandchildren with the condition. Female premutation carriers may also be at increased risk for earlier onset of menopause; however, premutation carriers may exist through several generations of a family and no symptoms of fragile X syndrome will appear.

The size of the premutation can expand over succeeding generations. Once the size of the premutation exceeds 230 repeats, it becomes a full mutation and the FMR-1 gene is disabled. Individuals who carry the full mutation may have fragile X syndrome. Since the FMR-1 gene is located on the X chromosome, males are more likely to develop symptoms than females. This is because males have only one copy of the X chromosome. Males who inherit the full mutation are expected to have mental impairment. A female's normal X chromosome may compensate for her chromosome with the fragile X **gene mutation**. Females who inherit the full mutation have an approximately 50% risk of mental impairment. The phenomenon of an expanding trinucleotide repeat in successive generations is called anticipation. Another unique aspect fragile X syndrome is that mosaicism is present in 15-20% those affected by the condition. Mosaicism is when there is the presence of cells of two different genetic materials in the same individual.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

CGG or CGG sequence—Shorthand for the DNA sequence: cytosine-guanine-guanine. Cytosine and guanine are two of the four molecules, otherwise called nucleic acids, that make up DNA.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

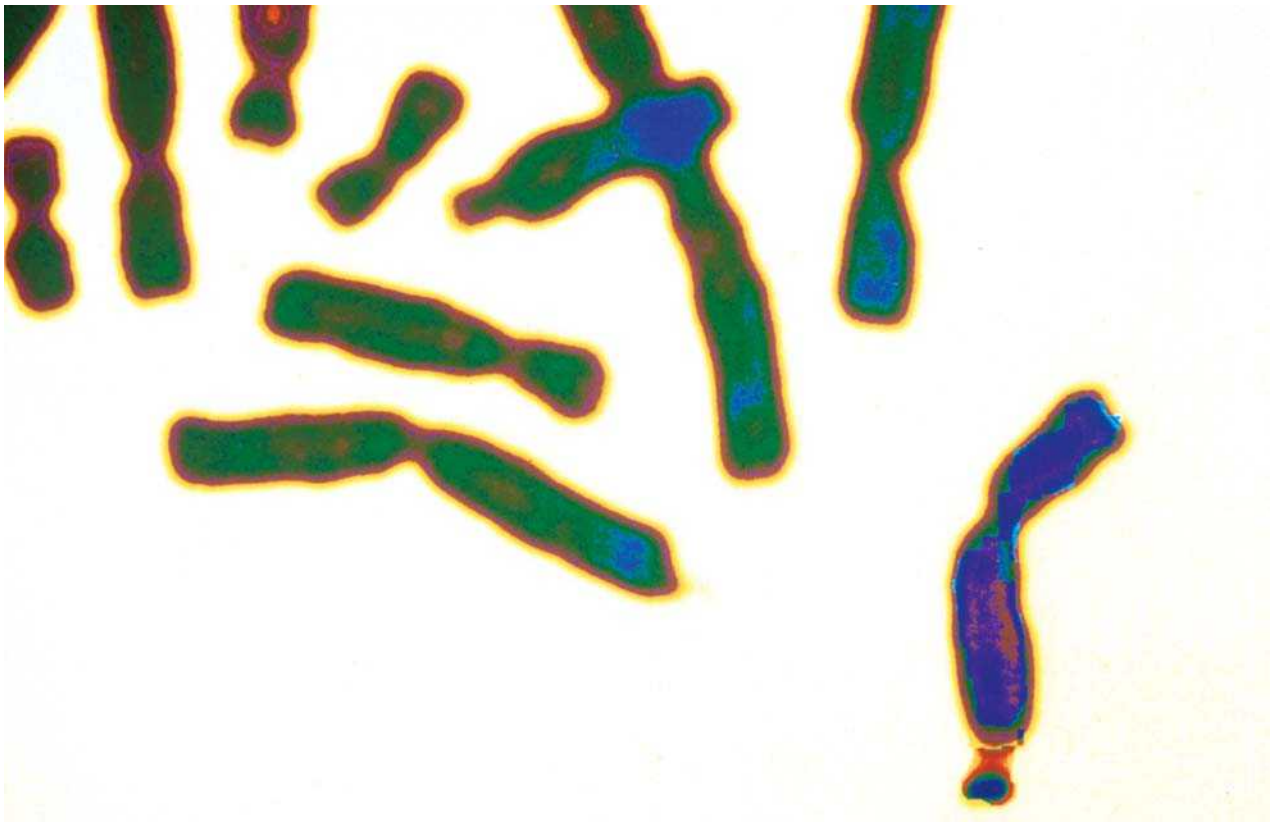
Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

FMR-1 gene—A gene found on the X chromosome. Its exact purpose is unknown, but it is suspected that the gene plays a role in brain development.

Mitral valve prolapse—A heart defect in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur but there are usually no symptoms.

Premutation—A change in a gene that precedes a mutation; this change does not alter the function of the gene.

X chromosome—One of the two sex chromosomes (the other is Y) containing genetic material that, among other things, determine a person's gender.



A fragile X chromosome is identifed as purple. *(Custom Medical Stock Photo, Inc.)*

Fragile X syndrome is inherited in an X-linked dominant manner (characters are transmitted by genes on the X chromosome). When a man carries a premutation on his X chromosome, it tends to be stable and usually will not expand if he passes it on to his daughters (he passes his Y chromosome to his sons). Thus, all of his daughters will be premutation carriers like he is. When a woman carries a premutation, it is unstable and can expand as she passes it on to her children; therefore, her grandchildren are at greater risk of developing the syndrome. There is a 50% risk for a premutation carrier female to transmit an abnormal mutation with each pregnancy. The likelihood for the premutation to expand is related to the number of repeats present; the higher the number of repeats, the greater the chance that the premutation will expand to a full mutation in the next generation. All mothers of a child with a full mutation are carriers of an FMR-1 gene expansion. Ninety-nine percent of patients with fragile X syndrome have a CGG expansion, and less than one percent have a point mutation or deletion on the FMR-1 gene.

Demographics

Fragile X syndrome affects males and females of all ethnic groups. It is estimated that there are about one in 4,000 to one in 6,250 males affected with fragile X syndrome. There are approximately half as many females with fragile X syndrome as there are males. The carrier frequency in unaffected females is one in 100 to one in 600, with one study finding a carrier frequency of one in 250.

Signs and symptoms

Individuals with fragile X syndrome appear normal at birth but their development is delayed. Most boys with fragile X syndrome have mental impairment. The severity of mental impairment ranges from learning disabilities to severe mental retardation. Behavioral problems include attention deficit and hyperactivity at a young age. Some may show aggressive behavior in adulthood. Short attention span, poor eye contact, delayed and disordered speech and language, emotional instability, and unusual hand mannerisms (hand flapping or hand biting) are also seen frequently. Characteristic physical traits appear later in childhood. These traits include a long and narrow face, prominent jaw, large ears, and enlarged testes. In females who carry a full mutation, the physical and behavioral features and mental retardation tend to be less severe. About 50% of females who have a full mutation are men-

tally retarded. Other behavioral characteristics include whirling, spinning, and occasionally **autism**.

Children with fragile X syndrome often have frequent ear and sinus infections. Nearsightedness and lazy eye are also common. Many babies with fragile X syndrome may have trouble with sucking and some experience digestive disorders that cause frequent gagging and vomiting. A small percentage of children with fragile X syndrome may experience seizures. Children with fragile X syndrome also tend to have loose joints which may result in joint dislocations. Some children develop a curvature in the spine, flat feet, and a heart condition known as mitral valve prolapse.

Diagnosis

Any child with signs of developmental delay of speech, language, or motor development with no known cause should be considered for fragile X testing, especially if there is a family history of the condition. Behavioral and developmental problems may indicate fragile X syndrome, particularly if there is a family history of mental retardation. Definitive identification of the fragile X syndrome is made by means of a genetic test to assess the number of CGG sequence repeats in the FMR-1 gene. Individuals with the premutation or full mutation may be identified through **genetic testing**. Genetic testing for the fragile X mutation can be done on the developing baby before birth through **amniocentesis** or chorionic villus sampling (CVS), and is 99% effective in detecting the condition due to trinucleotide repeat expansion. Prenatal testing should only be undertaken after the fragile X carrier status of the parents has been confirmed and the couple has been counseled regarding the risks of recurrence. While prenatal testing is possible to do with CVS, the results can be difficult to interpret and additional testing may be required.

Treatment and management

Presently there is no cure for fragile X syndrome. Management includes such approaches as speech therapy, occupational therapy, and physical therapy. The expertise of psychologists, special education teachers, and genetic counselors may also be beneficial. Drugs may be used to treat hyperactivity, seizures, and other problems. Establishing a regular routine, avoiding over stimulation, and using calming techniques may also help in the management of behavioral problems. Children with a troubled heart valve may need to see a heart specialist and take medications before surgery or dental procedures. Children with frequent ear and sinus infections may need to take medications or have special tubes placed in their ears to drain excess fluid. Mainstreaming of children with fragile X syndrome into regular classrooms is encouraged because they do well imitating behavior. Peer tutoring and positive reinforcement are also encouraged.

Prognosis

Early diagnosis and intensive intervention offer the best prognosis for individuals with fragile X syndrome. Adults with fragile X syndrome may benefit from vocational training and may need to live in a supervised setting. Life span is typically normal.

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Nada Quercia, MS, CCGC, CGC

Francois dyscemphalic syndrome *see* **Hallermann-Streiff syndrome**

Fraser syndrome

Definition

Fraser syndrome, also called cryptophthalmos with other malformations, is a rare non-sex linked (autosomal) recessive genetic disorder that primarily affects the eyes.

Description

Fraser syndrome is named for Canadian geneticist C. R. Fraser, who first described the syndrome in 1962. The syndrome is also referred to as crytophthalmos with other malformations because over 90% of the people born with this syndrome have hidden (crypto-) eyes (ophthalmos). It is alternately called cryptophthalmos-syndactyly syndrome since most affected individuals also have partial fusion or webbing of their fingers or toes (syndactyly).

Individuals affected with Fraser syndrome appear to have hidden eyes (cryptophthalmos) because the skin of their eyelids is partially or fully sealed shut. Cryptophthalmos is classified into three types: complete, in which the eyelid is completely fused over an existing eye; incomplete, in which the eyelid is only partially fused over the underlying eye; and abortive, in which the eyelid is completely fused and the underlying eye does not form.

Approximately half of all individuals affected with Fraser syndrome have abnormalities of the genitals, while 37% have kidney (renal) problems, including the lack of one or both kidneys. Some individuals also have abnormalities of the voice box (larynx) and of the middle and outer ear.

Genetic profile

The **gene** responsible for Fraser syndrome has not yet been identified, but it is known to be transmitted as a non-sex linked (autosomal) recessive trait. It seems likely that the gene responsible for Fraser syndrome alters the normally programmed cell death process (apoptosis) in affected individuals. This is suggested by the fact that several of the symptoms of Fraser syndrome result from a failure of apoptosis.

Cells are normally programmed to die when certain conditions have been met. These cells are then replaced by new cells in an ongoing process. **Cancer** cells do not have the ability to undergo this natural cell death process. It is for this reason that many cancers are associated with tumor growth. Tumors are made up of cells that do not undergo apoptosis. The cells in individuals with Fraser syndrome that do not seem to undergo apoptosis are those cells that cause the overgrowth of certain tissues, such as the eyelids in the case of cryptophthalmos or the tissues of the fingers and toes in the case of syndactyly.

Demographics

Fraser syndrome is very rare, occurring in fewer than one of every 100,000 births. It has been reported that the frequency of the syndrome is over 100 times higher in the Roma (gypsy) population as in the non-Roma population. As in all recessive **genetic disorders**, both parents must carry the **gene mutation** in order for their child to have the disorder. Approximately 15% of individuals diagnosed with Fraser syndrome have been observed in cases where the parents are related by blood (consanguineous). Parents with one child affected by Fraser syndrome have a 25% likelihood that their next child will also be affected with the disease. As of 2000, the specific gene mutations responsible for Fraser syndrome have not been identified.

Signs and symptoms

Fraser syndrome is characterized by hidden eyes (cryptophthalmos) resulting from either partial or complete fusion of the eyelids. This condition may be observed on only one side (unilaterally), but it is generally observed in both eyes of affected individuals (bilateral cryptophthalmos). In most cases the underlying eyes are not fully formed which causes small eyes (microphthalmia). In some cases of Fraser syndrome the underlying eyes are completely absent (abortive cryptophthalmos).

Individuals with Fraser syndrome have abnormal or absent tear ducts and widely spaced eyes (hypertelorism). Blindness from birth is quite common in affected individuals. However, in cases where there is a functioning visual pathway to the inner, light-sensitive layer of the eye (retina), partial vision has been observed.

Approximately half of those individuals affected with Fraser syndrome have partial or complete fusion of the fingers or toes (syndactyly). In cases of Fraser syndrome, the observed syndactyly is most often of the third and fourth digits of the hands or feet. An extra finger or toe situated outside the normal fifth digit (postaxial polydactyly) and webbing of the fingers or toes (cutaneous syndactyly) are also symptoms seen in individuals with Fraser syndrome. The only other bone abnormality seen with any high frequency is a greater than normal width of the cartilaginous joint between the pubic bones in the front of the pelvis (symphysis pubis).

Abnormalities of the middle and/or outer ear occur in approximately 50% of affected individuals. These symptoms range from malformations and closures of the outer ear (called the pinna or the auricle) to an absence of

the auditory canal (Eustachian tube). In cases where the Eustachian tube is absent, connective tissue fills the space where the auditory canal should be and bone covers what would be the opening of the auditory canal to the outer ear. As a result of these abnormalities, some individuals may be deaf or suffer from hearing problems.

Approximately 85% of those affected with Fraser syndrome have abnormalities of the nose. The most common nasal abnormalities are blockage or narrowing of the nasal cavities that open into the mouth and throat (the internal nares or choanae) by either excess bone or by membranous tissue. Forking of the tongue and cleavage of the internal nasal passage are also seen.

Blockage and narrowing of the voice box (larynx) are also commonly associated with Fraser syndrome. Occasionally an abnormal web-like structure is seen in the vocal apparatus of the larynx (glottis) that causes an inability of speech if not corrected.

Abnormalities of the digestive system, otherwise known as the gastrointestinal, or GI, tract are also common. These abnormalities include an incomplete development of the membrane (mesentery) that connects the small intestine to the back wall of the abdominal cavity; malrotation of the small intestine; a protrusion of parts of the large intestine through an abnormal opening in the abdominal wall near the navel (umbilical hernia); and, defects of the muscle beneath the lungs (diaphragm) that is responsible for the flow of air into and out of the lungs.

Approximately 50-80% of all individuals with Fraser syndrome have abnormalities of the genitalia. Affected females may have partial or complete fusion of the folds of skin on either side of the vagina (labia), an abnormally large clitoris, a malformation of the paired tubes that connect the ovaries to the uterus (fallopian tubes), and/or an abnormally shaped uterus (bicornate uterus). Affected females beyond puberty also may not have a menstrual cycle. In affected males, one or both testicles may fail to descend into the scrotum, the urinary opening may occur on the underside of the penis rather than at the tip of the penis (hypospadias), the penis may be abnormally small, and/or the urinary opening of the penis may be fused shut (anterior urethral atresia).

Another complication of Fraser syndrome is malformations of one or both kidneys. These malformations may include improper development (renal dysplasia), underdevelopment (renal hypoplasia), or the complete absence of one or both kidneys (unilateral or bilateral renal agenesis).

Both the navel and the nipples may develop in irregular locations. The navel can be located lower than normal and the nipples are generally wider set. A hairline that extends forward over the temples is an additional cosmetic symptom of Fraser syndrome.

KEY TERMS

Apoptosis—The normally programmed cell death process in which cells die in order to be replaced with new cells.

Atresia—An abnormal condition in which a structure that should be hollow is fused shut.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Consanguineous—Sharing a common bloodline or ancestor.

Cryptophthalmos—An abnormal formation of the eye in which the eyelid, or overlaying skin of the eye, is fused shut. Literally, "hidden eye."

Hypertelorism—A wider-than-normal space between the eyes.

Microphthalmia—Small or underdeveloped eyes.

Postaxial polydactyly—A condition in which an extra finger or toe is present outside of the normal fifth digit.

Renal agenesis—Absence or failure of one or both kidneys to develop normally.

Stenosis—The constricting or narrowing of an opening or passageway.

Syndactyly—Webbing or fusion between the fingers or toes.

Many infants with Fraser syndrome suffer from water on the brain (hydrocephaly) and some cases have been found in which one of the normal cavities within the brain (the left ventricle) is not present. Dandy-Walker syndrome, a brain malformation of the fourth ventricle of the brain, has also been associated with Fraser syndrome. These brain abnormalities can all cause mental retardation.

Diagnosis

The symptoms of Fraser syndrome have been classified into four major and eight minor characteristics. A patient is diagnosed with Fraser syndrome rather than another genetic syndrome by the presence of at least two of the four major characteristics of the syndrome accompanied by at least one of the eight minor characteristics of the syndrome, or by the presence of one major characteristic and at least four minor characteristics.

The four major characteristics of Fraser syndrome are hidden eyes (cryptophthalmos), fused or partially fused fingers and/or toes (syndactyly), abnormalities of the genitals, and the existence of an affected sibling.

The eight minor characteristics of Fraser syndrome are malformations of the nose, malformations of the ears, malformations of the voice box, a protrusion of parts of the large intestine through an abnormal opening in the abdominal wall near the navel (umbilical hernia), the absence or the incomplete development of one or both kidneys (renal agenesis), abnormalities of the bones other than syndactyly, cleavage of the tongue or other oral clefts, and mental retardation.

Prenatal diagnosis of Fraser syndrome is possible as early as 18 weeks into the pregnancy and is accomplished by the observance via ultrasound of a combination of some or all of the following conditions: blockage of urine flow out of the bladder; small eyes; fused or partially fused fingers and/or toes; blockage of the lungs (pulmonary obstruction) resulting from an absence or closure of the voice box (laryngeal atresia); the accumulation of thin, watery fluid (serous fluid) in the abdominal cavity (ascites); a blood disorder (fetal hydrops) that prevents proper formation of the oxygen-carrying molecule of blood (hemoglobin); a presence of an abnormally high amount of fluid in the tissues comprising the nape of the neck (nuchal edema), and an absence of amniotic fluid due to an incomplete development of the kidney (oligohydramnios).

Treatment and management

Genetic counseling is particularly important in the prenatal treatment and management of Fraser syndrome. This is because the severity of symptoms and appearance of an infant with this syndrome is likely to be very similar in a sibling also born with the disease.

Surgery is almost always necessary to correct the improperly fused tissues of the eyelids, ears, nose, and genitals. Most affected individuals are blind at birth, however, if some visual function is observed to be present, such as a wincing reaction to strong light, partial vision is possible after surgery to repair the damaged eyelids. Recently, corneal transplant surgery has been used to achieve improvements in vision. In cases of a missing eye (anophthalmia) reshaping of the eye socket may be necessary and a glass eye will need to be fitted for cosmetic purposes. Many infants diagnosed with Fraser syndrome are also deaf or partially deaf at birth. Special programs for the hearing and vision impaired will be necessary for these affected persons.

The most serious and life-threatening abnormalities associated with Fraser syndrome are those of the kidneys and the larynx. In some cases, the laryngeal malformations cannot be repaired, which leads to either stillbirth or death shortly after birth. This is particularly true of blockage of the larynx (laryngeal atresia). Corrective surgery is often possible in cases of narrowing of the larynx (laryngeal stenosis).

If both kidneys are absent (bilateral renal agenesis), the affected individual is usually stillborn. If only one kidney is present (unilateral renal agenesis), the kidney or kidneys are improperly developed (renal dysplasia), or underdeveloped (renal hypoplasia) the affected individual may require kidney dialysis or a kidney transplant. The abnormalities of the small intestine that are associated with Fraser syndrome are generally correctable through surgery.

Prognosis

The type and severity of the kidney and voice box malformations that may result in Fraser syndrome usually determine the prognosis. Overall, 25% of all babies born with Fraser syndrome are stillborn. Another 20% die within the first year of infancy, usually in the first few weeks of life. The cause of death is usually lack of kidney function or blockage of the larynx. Kidney and larynx defects tend to be either very slight or absent in the surviving 55% of Fraser syndrome affected individuals, but developmental delay is observed in most patients.

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Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

National Kidney Foundation. 30 East 33rd St., New York, NY 10016. (800) 622-9010. <http://www.kidney.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paul A. Johnson

FRDA-1 *see* **Friedreich ataxia**

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Distal arthrogryposis—A disorder characterized by contractions of the muscles in the hands.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Freeman-Sheldon syndrome

Definition

Freeman-Sheldon syndrome (FSS) is a very rare genetic disorder characterized by a small, puckered mouth, which gives the appearance of a person whistling. For this reason, Freeman-Sheldon syndrome is also known as whistling face syndrome. FSS may also be referred to as windmill vane hand syndrome or craniocarpotarsal dystrophy.

Description

Ernest Freeman and Joseph Sheldon, two British physicians, first described this distinct disorder in 1938. The syndrome is characterized by skeletal malformations in the hands and feet and facial abnormalities.

In addition to the small mouth, characteristics of FSS include a flat, mask-like face, underdeveloped nose cartilage, contracted muscles of the joints of fingers and hand, and clubbed feet. Most of the features of FSS are caused by muscle weakness. In addition to those characteristics noted above, individuals with FSS may also have crossed eyes, drooping upper eyelids, **scoliosis**, hearing loss, and walking difficulties. Intelligence is usually normal, health is generally good, and life expectancy is normal.

Genetic profile

Usually, FSS follows an autosomal dominant **inheritance** pattern. With this pattern of inheritance, the syndrome appears when a child inherits one defective **gene** from one parent. In some families, FSS follows an autosomal recessive inheritance pattern. In these cases, the condition only appears when a child receives the same defective gene from each parent. This syndrome can also occur sporadically, that is, neither parent passes on the gene responsible for FSS.

As of 2001, the gene responsible for FSS has not been located. Current genetic research is focusing on chromosome 11. Some experts consider FSS a form of distal arthrogryposis, which has been mapped to chromosome 11, specifically to location 11p15.5.

Demographics

Freeman-Sheldon syndrome is extremely rare. It affects males and females in equal numbers.

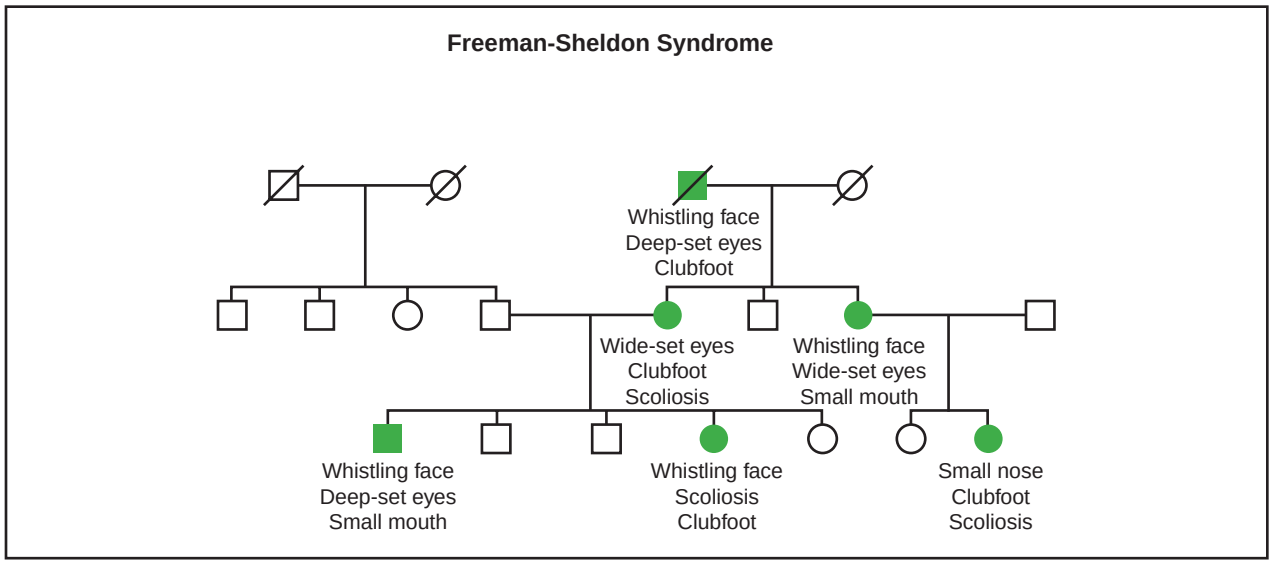
Signs and symptoms

Doctors can recognize Freeman-Sheldon syndrome at birth. Babies born with FSS usually have distinct abnormalities of the head, face, hands, and feet.

Facial abnormalities usually include an extremely small and puckered mouth, a full forehead, prominent cheeks, and thin, pursed lips. The middle part of the face may be flat, giving the baby a mask-like appearance. There may be a high palate, unusually small jaw, abnormally small tongue, and a raised mark or dimpling in the shape of an "H" or "V" on the chin. Other common facial abnormalities associated with FSS include widely-spaced, deep-set eyes, crossed eyes, and down-slanting eye openings.

Infants born with FSS may have malformations of the hands or feet, including clubbed feet. The muscles in the joints of the fingers and hands may be contracted.

Characteristics of FSS are often linked with other problems such as impaired speech, swallowing and eating difficulties, and vomiting. Children may fail to grow and gain weight at the expected rate, and there may be respiratory problems. Although most of the characteristics of FSS will be discovered fairly early in life, scoliosis (curvature of the spine) may be diagnosed later in childhood or adolescence as the child grows.



(Gale Group)

Diagnosis

As of 2001, there is no laboratory test to diagnose Freeman-Sheldon syndrome. Because many of the characteristics of FSS are present at birth, doctors can recognize and diagnose FSS following birth based on these characteristics. FSS has also been diagonsed prenatally using ultrasound imaging. Since the gene responsible for FSS has not yet been identified, chromosomal tests are not used in diagnosis.

Because FSS can run in families, parents of children with FSS may wish to seek **genetic counseling**.

Treatment and management

Most children with Freeman-Sheldon syndrome will require orthopedic or plastic surgery to correct their hand problems, clubbed feet, and tight mouth. Plastic surgery can improve the function and appearance of the mouth and nose. Craniofacial surgery can reshape the frontal bone and increase eyelid openings. A potential surgical complication in FSS patients is **malignant hyperthermia** (a serious problem with inhaled anesthetic agents). A muscle biopsy prior to surgery can rule out this risk. The thumb may be repositioned to improve hand function.

Prognosis

Life expectancy for infants diagnosed with Freeman-Sheldon syndrome is normal. Infants and children with FSS may be referred to physical and speech therapists. Physical therapy may help children improve the use of their hands, and it also can improve ambulation (walking). Speech therapy may improve tongue movement, which helps speech and swallowing. Sometimes, adaptive devices are recommended to aid muscular function.

Resources

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Lev, D., et al. "Progressive Neurological Deterioration in a Child with Distal Arthogryposis and Whistling Face." *Journal of Medical Genetics* 37 (2000): 231-233.

Ohyama, K., et al. "Freeman-Sheldon Syndrome: Case Management from Age 6 to 16 Years." *Cleft Palate Craniofacial Journal* 34 (1997): 151-153.

ORGANIZATIONS

Freeman-Sheldon Parent Support Group. 509 East Northmont Way, Salt Lake City, UT 84103-3324. (801) 364-7060.

Lisa Ann Fratt

Friedreich ataxia

Definition

Friedreich ataxia (FA) is an inherited, progressive nervous system disorder causing loss of balance and coordination.

Description

Ataxia is a condition marked by impaired coordination. Friedreich ataxia is the most common inherited ataxia, affecting between 3,000–5,000 people in the United States.

Genetic profile

FA is an autosomal recessive disease, which means that two defective **gene** copies must be inherited to develop symptoms, one from each parent. A person with only one defective gene copy is called a carrier and will not show signs of FA, but has a 50% chance of passing along the gene to offspring with each pregnancy. Couples in which both parents are carriers of FA have a 25% chance with each pregnancy of conceiving an affected child. The gene for FA is on chromosome 9 and codes for a protein called frataxin. Normal frataxin is found in the cellular energy structures known as mitochondria, where it is involved in regulating the transport of iron.

In approximately 96% of patients with FA, both copies of the frataxin gene are expanded with nonsense information known as a "triple repeat" of a particular sequence of **DNA** bases called "GAA". Normally, the GAA sequence is repeated between six and 34 times, but those with FA have between 67 and 1,700 copies. About 4% of patients have been found to have the triple repeat in only one copy of the frataxin gene and a different gene change in the other. Longer GAA repeats are associated with more severe disease, but the severity of disease in a particular individual cannot be predicted from the repeat length. The extra DNA or other gene change interferes with normal production of frataxin, thereby impairing iron transport. FA is thought to develop at least in part because defects in iron transport prevent efficient use of cellular energy supplies. Extra iron builds up in the mitochondria, leading to the accumulation of damaging chemicals called free-radicals.

The nerve cells most affected by FA are those in the spinal cord involved in relaying information between muscles and the brain. Tight control of movement requires complex feedback between the muscles promoting a movement, those restraining it, and the brain. Without this control, movements become uncoordinated, jerky, and inappropriate for the desired action.

Demographics

The prevalence of FA in the Caucasian population is approximately one in 50,000 to one in 25,000. Prevalence appears to be highest in Italy. Approximately 1% of Caucasian individuals carry one defective copy of the gene for frataxin. Friedreich ataxia is very rare in people of Asian or African descent.

KEY TERMS

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Congenital—Refers to a disorder which is present at birth.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Signs and symptoms

Symptoms of FA usually first appear between the ages of eight and 15, although onset as early as 18 months or as late as age 25 is possible. The first symptom is usually gait incoordination. For instance, a child with FA may graze doorways when passing through or trip over low obstacles. Unsteadiness when standing still and deterioration of position sense is common. Foot deformities and walking up off the heels often results from uneven muscle weakness in the legs. Muscle spasms and cramps may occur, especially at night.

Ataxia in the arms usually follows within several years, leading to decreased hand-eye coordination. Arm weakness does not usually occur until much later. Speech and swallowing difficulties are common. The loss of reflexes in the lower legs is common. **Diabetes mellitus**, a condition characterized by elevated blood sugar, may also occur. One study suggested that carriers of one FAA gene with an "intermediate" sized GAA region (10 to 36 copies of GAA) are also at increased risk for diabetes, but as of 2001, other similar studies did not show this finding. Nystagmus, or eye tremor, is common in FA, along with some loss of visual acuity. Hearing loss may also occur. A side-to-side curvature of the spine (**scoliosis**) occurs in many cases and may become severe.

Heart muscle enlargement with or without heartbeat abnormality occurs in about two thirds of FA patients, leading to shortness of breath after exertion, swelling in the lower limbs, and frequent complaints of cold feet.

There are some atypical forms of FA. For example, the Acadian population that descended from Northern France and now live in Louisiana, have a very slow progressing disease and rarely have heart problems, leading them to live longer than most patients with FA. Other forms include late onset Friedreich ataxia (LOFA), in which symptoms begin after the age of 25 years, and Friedreich ataxia with retained reflexes (FARR). All three of these forms have been shown to result from changes in the same gene as the "classic" form. There have been a few patients with classic FA described in which the

frataxin gene on chromosome 9 has been shown not to be the cause. A form of ataxia caused by a gene change resulting in vitamin E deficiency, but having similar symptoms to FA, has been identified with changes in a different gene on chromosome 8.

In 1988, a Spanish family was reported in which several members had FA along with congenital **glaucoma**, a disease caused by increased pressure inside the eye. Glaucoma is not normally seen in patients with Friedreich ataxia or other types of inherited ataxia. Most of the affected family members had parents who were closely related to each other, which placed children at increased risk for autosomal recessive conditions in general. Therefore, the glaucoma and FA may have been caused by two distinct genes inherited in an autosomal recessive manner. As of 2001, there was no follow-up of this family reported, so it is not known if their unusual disease was caused by a gene other than the since-identified frataxin gene or if the glaucoma and the FA were caused by two different genes.

Diagnosis

Diagnosis of FA involves a careful medical history and thorough neurological exam. Lab tests include electromyography, an electrical test of muscle, and a nerve conduction velocity test. An electrocardiogram may be performed to diagnose heart arrhythmia.

Direct DNA testing is available, allowing FA to be more easily distinguished from other types of ataxia. Testing is accomplished by counting the number of GAA repeats in the frataxin gene to see if there is an expansion (67 or more sets of the DNA bases GAA) and by looking for other gene changes in patients who only show a GAA expansion in one copy of the frataxin gene. As of 2001, no patient with FA has been reported to have non-GAA changes in both copies of the frataxin gene. Many of these non-GAA changes completely prevent the frataxin protein from being made, so having two copies may not be compatible with life. The same genetic test may be used to determine the presence of the genetic defect in the carrier state (i.e., one normal copy and one defective copy of the frataxin gene) in unaffected individuals, such as adult siblings, who would like to learn their chances of producing an affected child. During pregnancy, the DNA of a fetus can be tested using cells obtained from procedures called chorionic villi sampling (CVS), in which cells from the placenta are studied, and **amniocentesis**, in which skin cells from the amniotic fluid surrounding the baby are tested.

Treatment

As of 2001, there is no prevention or cure for FA, nor any proven treatment that can slow its progress. One recent (1999) study in three patients has suggested that a drug called idebenone can reduce heart problems. Idebenone is an antioxidant—a drug that captures free-radicals, the toxic chemicals generated by increased iron. Amantadine may provide some limited improvement in ataxic symptoms, but is not recommended in patients with cardiac abnormalities. Physical and occupational therapy are used to maintain range of motion in weakened muscles, and to design adaptive techniques and devices to compensate for loss of coordination and strength. Some patients find that using weights on the arms can help dampen the worst of the uncoordinated arm movements.

Heart problems and diabetes are treated with drugs specific to those conditions.

Prognosis

The rate of progression of FA is highly variable. Most patients lose the ability to walk within 15 years of symptom onset, and 95% require a wheelchair for mobility by age 45. Reduction in lifespan from FA complications, usually cardiac, is also quite variable. Average age at death, usually from heart problems, is in the mid-30s, but may be as late as the mid-60s. As of 2001, the particular length of the triple repeat has not been correlated strongly enough with disease progression to allow prediction of the course of the disease on this basis.

Resources

BOOKS

Isselbacher, Kurt J., et al., eds. "Spinocerebellar Degeneration (Friedreich's Ataxia)." In *Harrison's Principles of Internal Medicine.* New York: McGraw-Hill, 1994, p. 2285.

PERIODICALS

Delatycki, Martin B., Robert Williamson, and Susan M. Forrest. "Friedreich Ataxia: An Overview." *Journal of Medical Genetics* 37 (2000): 1-8.

ORGANIZATIONS

Friedreich's Ataxia Research Alliance. 2001 Jefferson Davis Highway #209, Arlington, VA 22202. (703) 413-4468. <http://www.frda.org>.

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

National Ataxia Foundation. 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447. (763) 553-0020. Fax: (763) 553-0167. naf@ataxia.org. <http://www.ataxia.org>.

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

Toni I. Pollin, MS, CGC

Frontonasal dysplasia

Definition

Frontonasal dysplasia, also called median cleft syndrome, is a rare disorder affecting primarily the face and head. The causes of frontonasal dysplasia are unknown. Most cases appear to occur randomly (sporadically), but it is suspected that some cases are genetically inherited. The term frontonasal dysplasia was first used in 1970 to describe this disorder.

Description

Frontonasal dysplasia is characterized by malformations of the central portion of the face, especially of the forehead, the nose, and the philtrum (the area between the nose and upper lip). A cleft, or divided area, that traverses one or more of the upper lip, philtrum, nose, and forehead is a hallmark of the disease. Occasionally, affected individuals also experience abnormalities of the brain, heart, and certain bones. In the most severe cases, mild to moderate mental retardation has been observed.

Genetic profile

Most cases of frontonasal dysplasia do not seem to show any genetic linkage. However, a case of an affected male with a spontaneous chromosome rearrangement, in which the abnormality was not inherited from either parent (a *de novo* rearrangement), involving **chromosomes** 3, 7, and 11 has been reported in the medical literature. From this case report, it is suggested that the search for the genetic mutation, or mutations, responsible for the appearance of frontonasal dysplasia should focus on locations 3q23, 3q27, 7q22.1, and 11q21. Other researchers have suggested an X-linked dominant trait or a non-sex linked (autosomal) recessive trait is responsible for genetic cases of frontonasal dysplasia. As of early 2001, further research into the genetic origin of this disorder is still needed.

Demographics

Frontonasal dysplasia is rare and statistical data on its occurrence has not been reported. It has not been associated with any particular ethnic or social group. Some reports show frontonasal dysplasia occurs twice as often in males as in females, and that it is associated with increased parental age, which points to chromosome mutation being a possible cause.

Signs and symptoms

Individuals affected with frontonasal dysplasia most often have widely spaced eyes (hypertelorism), a broadening of the nose (nasal root), absence of the skin that forms the tip of the nose, and a hairline that extends farther than normal and comes to a point in the center of the forehead (widow's peak). A cleft lip along the centerline (median cleft lip) of the skin between the nose and the upper lip (philtrum) is also generally seen in individuals affected with the condition.

In some cases, an individual diagnosed with frontonasal dysplasia may also have a vertical groove down the middle of the face; which, in the most extreme instances, may cause the nose to vertically separate into two parts (median cleft nose). Additionally, in some cases of frontonasal dysplasia, a skin-covered gap may be present in the bones of the forehead (anterior cranium bifidum occultum). In cases where the bone deformations of the nose and forehead are quite severe, there may be a malformation of the bony structures (orbits) that hold the eyeballs. Eye defects and even blindness may be present.

In a few cases of frontonasal dysplasia, the group of heart abnormalities known as the tetralogy of Fallot have been observed. This is a combination of four disorders of the heart: an abnormal narrowing of the valve that opens from the right ventricle of the heart into the pulmonary artery (pulmonary stenosis); a hole or perforation in the wall between the left and right ventricles of the heart that

KEY TERMS

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

***de novo* mutation**—Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

Hallucal polydactyly—The appearance of an extra great toe.

Hypertelorism—A wider-than-normal space between the eyes.

Philtrum—The center part of the face between the nose and lips that is usually depressed.

Tetralogy of Fallot—A congenital heart defect consisting of four (tetralogy) associated abnormalities: ventricular septal defect (VSD—hole in the wall separating the right and left ventricles); pulmonic stenosis (obstructed blood flow to the lungs); the aorta "overrides" the ventricular septal defect; and thickening (hypertrophy) of the right ventricle.

allows blood to flow directly from the higher pressure left ventricle to the lower pressure right ventricle (ventricular septal defect); abnormal positioning of the aorta on the right, rather than the left, side of the heart (dextroposition of the aorta) which means that blood flows out of the right ventricle into the aorta so that deoxygenated blood rather than oxygenated blood is being delivered to the body; and finally, an abnormally large right ventricle (hypertrophy of the right ventricle), which is generally associated with the three other anomalies since each of these over-burdens the right ventricle. This set of conditions leads to an improper oxygenation of the blood, causing "blue baby" at birth. When these defects are observed, surgery is required.

Skeletal deformities have also been observed in some cases of frontonasal dysplasia. These include the presence of an extra toe arising from the great toe (hallucal polydactyly) and a severe under-development of the major bone of the shin (tibial aplasia).

Brain anomalies are also associated with frontonasal dysplasia. These include the absence of the connection between the left and right hemispheres of the brain (corpus callosum) and swelling or hernias of the brain (basal **encephalocele**). In extreme cases of frontonasal dysplasia, mental retardation may be seen. The extent of retardation appears linked with the degree of hypertelorism, which is an abnormal increase of the distance between the eye sockets. The greater the observed distance between the eyes, the greater the likelihood of mental retardation or developmental delays.

Diagnosis

Frontonasal dysplasia is generally diagnosed at birth based on the observed facial abnormalities. A presence of two or more of the following symptoms is considered a positive diagnosis for frontonasal dysplasia: a skin-covered gap in the bones of the forehead (anterior cranium bifidum occultum); hypertelorism; median cleft lip; median cleft nose; and/or any abnormal development of the center (median cleft) of the face.

Because the genetic cause of frontonasal dysplasia remains unclear and because the majority of cases are sporadic, the only way to diagnose frontonasal dysplasia before birth (prenatally) is via ultrasound observation of craniofacial deformations (**holoprosencephaly**). This is a technique that produces pictures of the fetus.

Treatment and management

Cosmetic surgery to correct the facial defects associated with frontonasal dysplasia is recommended for all affected individuals. In severe cases, additional facial surgeries may be required after the initial surgery. These include reformation of the eyelids (canthoplasty), reformation of the orbits (orbitoplasty), surgical positioning of the eyebrows, and plastic surgery of the nose (rhinoplasty).

In cases of **congenital heart defects**, surgery to correct the defects is required shortly after birth.

Surgery is available to remove the extra toe seen in some affected individuals. Surgeries to correct underdevelopment of the tibia, or shin bone, may also be required. The tibia supports five-sixths of the body weight when a person is standing, with the smaller fibula supporting the remaining one-sixth. If surgery is not performed to correct the shin bone defects seen in some cases of frontonasal dysplasia, the affected individual may never be able to stand or walk.

In the rare instance of mental retardation associated with frontonasal dysplasia, early and continuing intervention programs may be necessary to assist the affected individual.

Prognosis

Individuals diagnosed with frontonasal dysplasia usually are of average intelligence and can expect a normal lifespan. In the rare cases of associated heart abnormalities, the affected individual may die shortly after birth if corrective surgery is not performed as soon as possible.

Resources

PERIODICALS

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Stevens, C., and M. Qumsiyeh. "Syndromal Frontonasal Dysostosis in a Child with a Complex Translocation Involving Chromosomes 3, 7, and 11." *American Journal of Medical Genetics* (February 1995): 494-7.

Trifiletti, R., et al. "Aicardi Syndrome with Multiple Tumors: A Case Report with Literature Review." *Brain Development* (July-August 1995): 283-5.

ORGANIZATIONS

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

FACES: The National Craniofacial Assocation. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

OMIM—Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?136760> (14 February 2001).

Reader's Digest Health—Frontonasal Dysplasia. <http://rdhealth.com/kbase/nord/nord809.htm> (14 February 2001).

Paul A. Johnson

Frontonasal malformation *see* **Frontonasal dysplasia**

Fryns syndrome

Definition

Fryns syndrome is a multiple congenital anomaly syndrome usually resulting in neonatal death.

Description

Fryns syndrome is a genetic condition involving abnormalities in many organ systems that usually results in neonatal death. The condition was first reported in 1979 by J. P. Fryns.

Typical anomalies include a characteristic facial appearance, including a broad nasal bridge (part of the nose between the eyes), small jaw, abnormal ears, cleft palate, abnormal fingers, underdevelopment of the lungs, and abnormalities of the urogenital system (kidneys and genitals). Diaphragmatic hernia (opening in the diaphragm muscle that can allow contents of the lower abdomen like the liver or intestine or stomach to move up into the chest cavity through the hole) can also be seen in some cases. Some researchers believe that there may be a distinct subset of patients without diaphragmatic hernia who are more mildly affected.

Genetic profile

Fryns syndrome is inherited in an autosomal recessive manner. This means that two defective **gene** copies must be inherited, one from each parent, for the disease to manifest itself. Persons with only one **gene mutation** are carriers for the disorder. A person who is a carrier for Fryns syndrome does not have any symptoms and does not know he/she is a carrier unless he/she has had a child with Fryns syndrome. Carrier testing is not available since the gene location is not known at this time. The likelihood that each member of a couple would be a carrier for a mutation in the same gene is higher in people who are related (called consanguineous). When both parents are carriers for Fryns syndrome, there is a one in four chance (25%) in each pregnancy for a child to have the disease. There is a two in three chance that a healthy sibling of an affected child is a carrier.

There have been several different chromosome abnormalities reported with a Fryns syndrome-like appearance. Investigation for a candidate gene causing Fryns syndrome has not yet identified the causative gene.

Demographics

The number of affected individuals is reported as seven in 100,000. There does not appear to be any ethnic difference in prevalence. As of 2001, there were more than 50 documented cases of Fryns syndrome in the literature.

Signs and symptoms

The most frequent anomalies have been described as diaphragmatic defects, underdeveloped lungs, **cleft lip and palate** (usually on both sides, called bilateral), heart defects, cysts in the kidneys, urinary tract abnormalities, and limb underdevelopment.

Most patients also have underdeveloped external genitals, abnormal internal reproductive structures, abnormalities in the digestive tract, and abnormalities in the structure of the brain. Fewer patients have eye abnormalities.

Other reported anomalies include fetal hydops (fluid surrounding the fetus prenatally, usually fatal), prematurity, **scoliosis** (curvature of the spine), extra vertebrae or ribs, abnormal bone formation, and small chest cavity.

Diagnosis

Prenatal diagnosis has been possible in several fetuses by use of ultrasound to identify in one fetus fetal hydrops, diaphragmatic hernia, and dilation of the cerebral ventricles and in another with cystic hygroma and diaphragmatic hernia. These anomalies themselves can be isolated or as a part of another genetic syndrome; it is the specific combination of anomalies that would lead one to suspect Fryns syndrome. Definitive diagnosis is not possible until after birth or autopsy.

Treatment and management

Since Fryns syndrome is a genetic disease, caused by mutations in specific genes, there is no cure at this time. Some of the anomalies may be amenable to surgery, such as diaphragmatic hernia or cleft palate, but the entire prognosis for the baby must be considered.

Special education for mentally retarded individuals is indicated if the child survives.

Prognosis

Unfortunately, the prognosis for babies with Fryns syndrome is poor, with usual neonatal death occurring due to the lung hyperplasia and respiratory distress or other anomalies. Approximately 14% of infants survive the neonatal period. Survivors typically do not have complex heart malformations and less frequently have diaphragmatic hernias, milder lung hypoplasia, and neurologic impairment (usually severe to profound mental retardation with serious brain malformations).

Resources

PERIODICALS

Ramsing, M., et al. "Variability in the Phenotypic Expression of Fryns Syndrome: A Report of Two Sibships." *American Journal of Medical Genetics* 95 (2000): 415.

ORGANIZATIONS

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937 info@geneticalliance. <http://www.geneticalliance.org>.

SHARE-Pregnancy and Infant Loss Support, Inc. St Joseph Health Center, 300 First Capital Dr., St. Charles, MO 63301. (800) 821-6819.

WEBSITES

Online Mendelian inheritance in Man (OMIM). <http://www.ncbi.nlm.nig.gov>.

Amy Vance, MS, CGC

FSH muscular dystrophy

Definition

The term **muscular dystrophy** refers to a group of conditions characterized by progressive muscle weakness and atrophy (deterioration). Many different types of muscular dystrophy have been described, each of which have unique features and usually a unique underlying genetic cause. Facioscapulohumeral (FSH) muscular dystrophy affects the muscles of the face and shoulders first. Usually the first signs of weakness appear before the age of 20 years. The symptoms of FSH muscular dystrophy are variable and are not fatal. One in five people who are affected require a wheelchair after the age of 40 years.

Description

Facio refers to the face, *scapulo* to the shoulder blades, and *humeral* to the bone of the upper arm. The symptoms of FSH muscular dystrophy are quite variable, even within the same family. Some individuals who have the altered **DNA** sequence never develop noticeable symptoms. Most people with the condition first notice weakness in their teenage years. Muscles of the shoulders and face are usually the first to be affected. These may remain the only parts of the body that are affected, or the weakness may progress to include the pelvic muscles, the lower limbs, and the hands. Intelligence and life expectancy are not affected.

Genetic profile

FSH muscular dystrophy has autosomal dominant **inheritance**. This means that an affected person has a 50% chance, with each pregnancy, to pass the altered **gene** on to the child. Every person has two copies of every DNA sequence, one inherited maternally and the other inherited paternally. The altered DNA sequence that causes FSH muscular dystrophy is on chromosome 4. If a person has one normal sequence and one altered sequence, he or she will probably develop FSH muscular dystrophy.

When an autosomal dominant condition is present in multiple generations of a family, usually someone from each generation is affected. If a person is the first in his or her family to have an autosomal dominant condition, doctors often assume that the gene mutated for the first time in the egg or sperm that came together to make that person. (This is called a new mutation.) However, when the physical symptoms associated with an altered gene are highly variable, the distinction between these two scenarios is less obvious.

The term non-penetrance refers to altered genes that do not always cause a person to have the typical associated symptoms. FSH muscular dystrophy is non-penetrant in some individuals. Therefore, an individual who appears to be the first person affected in his or her family may have actually inherited the mutated DNA sequence from his or her mother or father. If so, his or her siblings would be at a 50% risk to also have inherited the altered sequence. Similarly, a mildly affected individual may have a child who is severely affected. Occasionally, two affected siblings are born to unaffected parents because of a genetic process called germline mosaicism.

Describing the genetics of FSH muscular dystrophy is slightly complicated by an interesting phenomenon. Genes are the DNA sequences that give the body instructions for growth, development, and functioning. Usually a mutation that causes a disease occurs in the gene associated with that disease. The above description refers to the mutation in FSH muscular dystrophy as an altered DNA sequence because it does not appear that this

sequence is actually part of a gene. The mutated sequence affects the gene for FSH muscular dystrophy, but probably is not part of the gene itself.

Demographics

The incidence of FSH muscular dystrophy is approximately 1/20,000. Some references report a lower incidence. Individuals from all ethnic groups are affected.

Signs and symptoms

The severity of the symptoms of FSH muscular dystrophy is highly variable. Some people are debilitated while others are minimally affected. Symptoms of progressive muscle weakness are usually first noticed in the teenage years, but may be noticed much later. For unknown reasons, more males than females with FSH muscular dystrophy develop symptoms by the age of 30 years. Specific muscle groups are affected. FSH muscular dystrophy does not lead to reduced sensation, nor does it affect intelligence.

Progressive muscle weakness of the shoulders/upper arms and face muscles are usually noticed first. The facial muscle weakness may be noticed as difficulty puckering the lips, smiling, sucking a straw, and closing the eyes while sleeping. Weakness may be asymmetrical, i.e., one shoulder may be weaker than the other shoulder. As the condition progresses, the muscles of the lower legs, abdomen, and hips may also become weak. The muscle weakness leads to abnormal positioning such as forward-sloping shoulders and exaggerated curvature of the spine. Although the weakness progresses continuously, the affected individual may perceive it as progressing rapidly at times and slowly at other times. This is because he or she notices the weakness when it results in loss of function. Reflexes are often weaker than normal. Twenty percent of affected individuals eventually require wheelchairs.

Describing the weakness as shoulder weakness or facial weakness is an oversimplification. In FSH muscular dystrophy, very specific muscles are affected. Not all of the facial muscles are affected, and not all of the muscles of the shoulder are affected. For example, the biceps and triceps of the upper arm are affected before the deltoids, and the forearm is relatively unaffected.

Some researchers report that more males than females with FSH muscular dystrophy develop symptoms by the age of 30 years. The reasons for this are unknown. Other researchers report that men and women are equally affected. Autosomal dominant conditions such as FSH muscular dystrophy usually affect men and women equally.

KEY TERMS

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genome—All of the DNA in one cell.

Germ line mosaicism—A rare event that occurs when one parent carries an altered gene mutation that affects his or her germ line cells (either the egg or sperm cells) but is not found in the somatic (body) cells.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Many individuals with early–onset FSH muscular dystrophy develop hearing loss of the high tones. Some individuals have more significant hearing loss. Slight changes of the retina are also a symptom of FSH muscular dystrophy. These changes usually do not affect vision.

A subset of FSH muscular dystrophy patients are severely affected. Individuals with severe infantile FSH muscular dystrophy are symptomatic at birth.

Diagnosis

The diagnosis of FSH muscular dystrophy is based on clinical history (symptoms), family history, and **genetic testing**. Many evaluations may be necessary to confirm the diagnosis. A thorough physical examination will be performed. Additional testing may include measuring the level of creatine kinase (CK) in the blood, special analysis of tissue obtained by muscle biopsy, and electromyogram (EMG). Sometimes it is difficult to rule out other possible causes of the muscle weakness.

Genetic testing is available for FSH muscular dystrophy, but it is complicated. Not everyone who is shown to have the associated abnormality of chromosome 4 develops symptoms of FSH muscular dystrophy. Alternately, not everyone who has FSH muscular dystrophy shows the typical genetic abnormality. Therefore, the test is helpful, but it must be interpreted in the context of the individual's medical history. A small subset of people tested will have inconclusive results. This is not due to lab error; some people have a genetic change that is midway between normal and abnormal.

Genetic testing can be performed on fetal cells that are obtained by **amniocentesis**, performed after the six-

teenth week of pregnancy, or chorionic villus sampling (CVS). CVS is usually performed between 10 and 12 weeks of pregnancy.

Researchers have shown some correlation between the type of mutation in the FSH region of chromosome 4 and the severity of the disease. Abnormal genetic results fall into a range from nearly normal or far from normal. People with certain abnormal genetic testing results tend to have earlier onset of symptoms and more rapidly progressive muscle weakness. Although many researchers have observed this correlation, the cause and effect relationship is not clear.

Because of the variable severity of symptoms, assumptions should not be made about the family history. A thorough clinical examination by an experienced physician may show that a person believed to be unaffected actually has mild symptoms.

Treatment and management

As of 2001, there is no effective treatment, prevention, or cure for FSH muscular dystrophy. Available treatments help affected persons with the effects of the disease but do not treat the disease itself. Supportive therapies include orthodic devices such as splints and braces, and sometimes surgery. Physical and occupational therapy may be helpful to ease discomfort and adjust to physical changes. Researchers continue to study various medications. Previous studies indicated that prednisone may improve muscle strength. However, this was not confirmed in more recent studies. Another medication, albuterol, was shown to be beneficial in early studies. Preliminary results of follow–up studies will be available in 2001 or 2002.

Prognosis

The prognosis for FSH muscular dystrophy is extremely variable. Prognosis cannot be predicted based on family history. Most people remain ambulatory, but some do not. Progression is usually slow. One third of affected individuals over 40 years of age have mild symptoms. A few people with FSH muscular dystrophy never develop muscle weakness. The typical course is weakness that becomes noticeable before the age of 20 years and progresses slowly but continuously throughout life.

Although FSH muscular dystrophy is rare in the general population, it is a relatively common neuromuscular disorder. Identification of the altered DNA sequence associated with FSH muscular dystrophy has stimulated research efforts. If the mechanism underlying the disease practice is discovered, researchers can better study possible treatments.

Resources

ORGANIZATIONS

FacioScapuloHumeral Society, Inc. 3 Westwood Rd., Lexington, MA 02420. (781) 860-0501. carol.perez @fshsociety.org. <http://www.fshsociety.org>.

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

Muscular Dystrophy Campaign. 7-11 Prescott Place, London, SW4 6BS. UK +44(0) 7720 8055. info@muscular-dystrophy.org. <http://www.muscular-dystrophy.org>.

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Michelle Queneau Bosworth, MS, CGC

G

Galacktokinase deficiency

Definition

Galactokinase deficiency is a one of a set of three distinct autosomal recessive-inherited disorders that causes **galactosemia**, or build up of the dietary sugar galactose in the body as a result of inborn errors of metabolism. This relatively rare form of the galactosemia disorder can lead to toxic injury to the eyes unless all forms of galactose, found chiefly in dairy products, are eliminated from the diet early in life.

Description

Lactose, the principle carbohydrate of human milk, commercial infant formulas, and other dairy products, is broken down in the human intestine into its component sugars: glucose and galactose. After absorption by the intestine, galactose is sequentially metabolized by three separate enzymes (galactokinase, galactose-1-phosphate uridyl transferase, and galactose-4-epimerase) to convert it to glucose, a usable form of fuel for individual cells.

The term, galactosemia, denotes the abnormally elevated level of galactose in the blood and body tissues that results when any of these three enzymes are missing or defective. Thus, inherited defects in any one of these three enzymes will result in galactosemia.

Classic galactosemia, the most common form of galactosemia, is due to the deficiency of the second enzyme in the pathway, galactose-1-phosphate uridyl transferase (GALT), and is typically associated with cataract formation, mental retardation, and liver damage. Galactokinase deficiency (also known as GALK deficiency, or Galactosemia Type II) is a rarer form of galactosemia caused by the absence of the enzyme, galactokinase, which is responsible for the first step of the conversion of galactose to glucose. However, unlike the more serious form of classic galactosemia, galactokinase deficiency mainly manifests as injury to the eyes without damage to other organ systems. The third and final form of galactosemia, uridine-diphosphate galactose-4-epimerase deficiency, is the rarest of the group; few cases have been described, and the symptoms of this form of galactosemia are variable, but usually mild.

Galactosemia may have been described in German medical publications as early as 1908, and in 1917, F. Goeppert noted symptoms of galactosemia in an infant and sibling, suggesting that the disorder could be inherited. In 1935, the American scientists H. H. Mason and M. F. Turner described a patient with a group of symptoms that could be prevented by removal of milk from the diet. In 1954, the individual steps in the metabolic pathway for the conversion of galactose to glucose was described by L. F. Leloir, who was later awarded a Nobel Prize in Chemistry for his efforts. Leloir's work made it possible for scientists, such as V. Schwatz and K. J. Isselbacher to demonstrate that defects in this metabolic pathway were responsible for galactosemia and its associated symptoms.

Genetic profile

Galactokinase deficiency, like other causes of galactosemia, is transmitted as an autosomal recessive trait. Individuals that are heterozygous for the defective allele have half the normal enzyme levels, which is still sufficient to convert all of their dietary galactose to glucose. Thus, heterozygotes experience neither galactosemia nor its symptoms.

Using advanced scientific techniques, the location of a **gene** that encodes for the galactokinase enzyme (GALK1) was localized to the human chromosome 17 (17p24) by D. Stambolian in 1995. At least 13 different types of mutations in the GALK1 gene have been identified that result in a nonfunctional galactokinase enzyme. A second human galactokinase gene (GK2), located on human chromosome 15, was also identified in 1992 by R. T. Lee. However, it is unclear whether this second gene plays an active role in galactose metabolism.

KEY TERMS

Allele—One of two or more alternate forms of a gene.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Galactitol—An alcohol derivative of galactose that builds up in the lens and causes cataracts.

Galactose—One of the two simple sugars, together with glucose, that makes up the protein, lactose, found in milk. Galactose can be toxic in high levels.

Galactosemia—Abnormally high levels of galactose in the blood due to an inherited defect in the conversion of galactose to glucose.

Galactosuria—High levels of galactose found in the urine that is seen with galactosemia.

Glucose—One of the two simple sugars, together with galactose, that makes up the protein, lactose, found in milk. Glucose is the form of sugar that is usable by the body to generate energy.

Heterozygous—Having two different versions of the same gene.

Lactose—A sugar made up of of glucose and galactose. It is the primary sugar in milk.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Newborn screening—The act of testing all infants for a specific disease shortly after birth for the purpose of preventing disease progression through prompt medical treatment.

Phenylketornuria (PKU)—An inborn error of metabolism that causes buildup of the amino acid, phenylalanine, in the body. The first disease to be used for newborn screening.

Pseudotumor cerebri—A syndrome of raised pressure within the skull that may cause vomiting, headache, and double vision.

Demographics

Galactokinase deficiency has an estimated incidence ranging from one in 500,000 to one in one million births and is much more rare than classic galactosemia. However, there is evidence that this trait may be unevenly distributed between various ethic and geographical groups. In 1967, R. Gitzelman characterized galactokinase deficiency in two related Romani (Gypsy) individuals. Later, in 1999, L. Kalaydijeva studied six Gypsy families from Bulgaria with galactokinase deficiency and found the same specific mutation in all cases. It was estimated that the carrier rate of the mutation in this population was as high as 5%, and Kalaydijeva suggested that this same mutation was likely responsible for the cases originally described by Gitzelman in 1967. As a result of the widespread prevalence of this mutation, incidence of galactokinase deficiency in Bulgaria has been reported to be one in 50,000 and among the Gypsy population, even higher, at one in 2,000.

The mutant galactokinase gene also shows higher prevalence in several other groups. In 1982, M. Magnani estimated the heterozygote frequency in Italy to be one in 310. In 1972, T. A. Tedesco presented evidence that African-Americans have an allele in high frequency that causes a decrease in red cell galactokinase activity that is likely different from the mutant allele that causes galactokinase deficiency. This finding was confirmed in 1988, when T. Soni found the same mutation in a group of African-Americans living in Philadelphia.

Signs and symptoms

Galactokinase deficiency is associated with galactosemia and cataracts (clouding of the lens of the eyes resulting in blurred vision), but without the systemic manifestations of liver disease and severe mental retardation that are commonly found in classic galactosemia. The cause of the cataract is an accumulation of galactitol (sugar alcohol derivative of galactose) within the lens of the eye. This galactitol accumulation attracts water, resulting in swelling and damage of the lens fiber.

There are infrequent reports of mild mental retardation in people with galactokinase deficiency, but the overwhelming majority of people have been shown to have normal intelligence. The rare finding of pseudotumor cerebri (a syndrome of raised pressure within the skull) has also been reported. Several investigators have reported premature development of cataracts (between the ages of 20 and 40 years old), even in individuals who are heterozygous for the galactokinase deficiency mutation.

Diagnosis

Newborn screening is the act of testing all infants for a specific disease shortly after birth for the purpose of preventing disease progression through prompt medical treatment. When newborn screening for the inherited disease **phenylketonuria (PKU)**, began in 1962, it quickly became clear that many infants with PKU were being identified for early treatment and that the mental retardation caused by the disease was being prevented.

This success encouraged R. Guthrie and others to consider additional metabolic disorders that might benefit from newborn screening. Since restricting dietary galactose early in life would prevent the development of irreversible symptoms, galactosemia appeared to be an ideal candidate for newborn screening. In 1963, Guthrie and his colleague, K. Paigen, developed a method to detect galactosemia that could be applied to the newborn blood specimen, and screening for galactosemia in the newborn became practical.

When trying to establish a diagnosis of galactokinase deficiency, an initial test is performed to detect galactosuria, or high levels of galactose in the urine that is seen with galactosemia. If that test proves positive, the next step is to determine which of the three enzymes needed to convert galactose to glucose is defective. When looking for galactokinase deficiency, blood samples are taken, and galactokinase activity is measured from red blood cells. If galactokinase activity is low, then the person has galactokinase deficiency. Thus, the diagnosis is made by demonstrating the deficiency of galactokinase in red blood cells and can be further confirmed by showing normal levels of the other two enzymes involved in this pathway using other tests. The disease can also be diagnosed before birth by testing fluid surrounding the unborn fetus for high levels of galactose, but this is rarely done.

Before widespread institution of newborn screening, these diagnostic tests were performed in infants with symptoms consistent with any form of galactosemia. As of the year 2000, newborn screening is mandated by law in every U.S. state except Louisiana, Pennsylvania, and Washington state.

Treatment and management

The galactosemia syndromes are effectively treated by rigid dietary exclusion of all lactose and galactose, primarily involving the elimination of milk and its products. A galactose-free diet should be initiated as early as possible, particularly because cataract formation may be reversed in early stages. Non-lactose milk substitutes are often used. Although soybean preparations contain bound galactose, they appear to be well-tolerated because the bound galactose is not readily absorbed by the intestine.

This galactose-free diet must be followed for life and requires close supervision, normally overseen by a team of health care professionals including a primary care provider, specialist physician, and a nutritionist. Periodic blood or urine measurements of galactose can be performed to monitor compliance with the restricted diet. Even with early diagnosis and strict dietary restrictions, people with galactosemia are at increased risk for cataract development in adulthood and should have regular eye examinations.

One detrimental effect of eliminating milk and milk products from the diet is the loss of adequate intake of vital nutrients such as protein, calcium, phosphorus, and riboflavin. As a result, nutritional deficiencies may develop, resulting in poor growth. Great care must be taken to achieve adequate daily supplementation with these nutrients after an infant is weaned from the enriched non-dairy formula. However, studies have demonstrated that children, adolescents, and adults often fail to routinely take prescribed supplements.

It also should be noted that exclusion of milk and milk products alone does not constitute a galactose-restricted diet, as galactose is found in other foods as well. Some fruits and vegetables with higher galactose content must also be avoided. Education of parents and children regarding galactose content of specific foods is important, and lists of foods can be obtained from nutritionists that prove useful in management.

Prognosis

Abundant experience with early treatment supports the concept that effective treatment instituted in the initial weeks of life can prevent all symptoms of the disease. In the rare event that some degree of mild retardation results, it is likely irreversible. Cataracts appear to be reversible if treatment is started within the initial three months of life.

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Parents of Galactosemic Children, Inc. 1100 West 49th St., Austin, TX 78756-3199. (512)458-7111. <http://www.tdh.state.tx.us/newborn/galac_1.htm>.

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Oren Traub, MD, PhD

Galactose-1-phosphate uridyl transferase deficiency *see* **Galactosemia**

Galactosemia

Definition

Galactosemia is an inherited disease in which the transformation of galactose to glucose is blocked, allowing galactose to increase to toxic levels in the body. If galactosemia is untreated, high levels of galactose cause vomiting, diarrhea, lethargy, low blood sugar, brain damage, jaundice, liver enlargement, cataracts, susceptibility to infection, and death.

Description

Galactosemia is a rare but potentially life-threatening disease that results from the inability to metabolize galactose. Serious consequences from galactosemia can be prevented by screening newborns at birth with a simple blood test.

Galactosemia is an inborn error of metabolism. "Metabolism" refers to all chemical reactions that take place in living organisms. A metabolic pathway is a series of reactions where the product of each step in the series is the starting material for the next step. Enzymes are the chemicals that help the reactions occur. Their ability to function depends on their structure, and their structure is determined by the deoxyribonucleic acid (**DNA**) sequence of the genes that encode them. Inborn errors of metabolism are caused by mutations in these genes which do not allow the enzymes to function properly.

Sugars are sometimes called "the energy molecules," and galactose and glucose are both sugars. For galactose to be utilized for energy, it must be transformed into something that can enter the metabolic pathway that converts glucose into energy (plus water and carbon dioxide). This is important for infants because they typically get most of their nutrient energy from milk, which contains a high level of galactose. Each molecule of lactose, the major sugar constituent of milk, is made up of a molecule of galactose and a molecule of glucose, and so galactose makes up 20% of the energy source of a typical infant's diet.

Three enzymes are required to convert galactose into glucose-1-phosphate (a phosphorylated glucose that can enter the metabolic pathway that turns glucose into energy). Each of these three enzymes is encoded by a separate **gene**. If any of these enzymes fail to function, galactose build-up and galactosemia result. Thus, there are three types of galactosemia with a different gene responsible for each.

Genetic profile

Every cell in a person's body has two copies of each gene. Each of the forms of galactosemia is inherited as a recessive trait, which means that galactosemia is only present in individuals with two mutated copies of one of the three genes. This also means that carriers, with only one copy of a **gene mutation**, will not be aware that they are carrying a mutation (unless they have had a genetic test), as it is masked by the normal gene they also carry and the fact that they have no symptoms of the disease. For each step in the conversion of galactose to glucose, if only one of the two copies of the gene controlling that step is normal (i.e. for carriers), enough functional enzyme is made so that the pathway is not blocked at that step. If a person has galactosemia, both copies of the gene coding for one of the enzymes required to convert glucose to galactose are defective and the pathway becomes blocked. If two carriers of the same defective gene have children, the chance of any of their children getting galactosemia (the chance of a child getting two copies of the defective gene) is 25% (one in four) for each pregnancy.

Demographics

Classic galactosemia occurs in the United States about one in every 50,000–70,000 live births.

Signs and symptoms

Galactosemia I

Galactosemia I (also called classic galactosemia), the first form to be discovered, is caused by abnormalities in both copies of the gene that codes for an enzyme called

galactose-1-phosphate uridyl transferase (GALT). There are 30 known different mutations in this gene that cause GALT to malfunction.

Newborns with galactosemia I appear normal at birth, but begin to develop symptoms after they are given milk for the first time. Symptoms include vomiting, diarrhea, lethargy (sluggishness or fatigue), low blood glucose, jaundice (a yellowing of the skin and eyes), enlarged liver, protein and amino acids in the urine, and susceptibility to infection, especially from gram negative bacteria. Cataracts (a grayish white film on the eye lens) can appear within a few days after birth. People with galactosemia frequently have symptoms as they grow older even though they have been given a galactose-free diet. These symptoms include speech disorders, cataracts, ovarian atrophy and infertility in females, learning disabilities, and behavioral problems.

Galactosemia II

Galactosemia II is caused by changes in both copies of the gene that codes for an enzyme called galactokinase (GALK). The frequency of occurrence of galactosemia II is about one in 100,000–155,000 births.

Galactosemia II is less harmful than galactosemia I. Babies born with galactosemia II will develop cataracts at an early age unless they are given a galactose-free diet. They do not generally suffer from liver damage or neurologic disturbances.

Galactosemia III

Galactosemia III is caused by changes in the gene that codes for an enzyme called uridyl diphosphogalactose-4-epimerase (GALE). This form of galactosemia is very rare.

There are two forms of galactosemia III: a severe form, which is exceedingly rare, and a benign form. The benign form has no symptoms and requires no special diet. However, newborns with galactosemia III, including the benign form, have high levels of galactose-1-phosphate that show up on the initial screenings for elevated galactose and galactose-1-phosphate. This situation illustrates one aspect of the importance of follow-up enzyme function tests. Tests showing normal levels of GALT and GALK allow people affected by the benign form of galactosemia III to enjoy a normal diet.

The severe form has symptoms similar to those of galactosemia I, but with more severe neurological problems, including seizures. Only two cases of this rare form had been reported as of 1997.

Diagnosis

The newborn screening test for classic galactosemia is quick and straightforward; all but three states require testing on all newborns. Blood from a baby who is two to three days old is usually screened for high levels of galactose and galactose-1-phosphate. If either of these compounds is elevated, further tests are performed to find out which enzymes (GALT, GALK, or GALE) are present or missing. DNA testing may also be performed to confirm the diagnosis.

If there is a strong suspicion that a baby has galactosemia, galactose is removed from their diet right away. In this case, an initial screen for galactose or galactose-1-phosphate will be meaningless. In the absence of galactose in the diet, this test will be negative whether the baby has galactosemia or not. In this case, tests to measure enzyme levels must be given to find out if the suspected baby is indeed galactosemic.

KEY TERMS

Casein hydrolysate—A preparation made from the milk protein casein, which is hydrolyzed to break it down into its constituent amino acids. Amino acids are the building blocks of proteins.

Catalyst—A substance that changes the rate of a chemical reaction, but is not physically changed by the process.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Galactose—One of the two simple sugars, together with glucose, that makes up the protein, lactose, found in milk. Galactose can be toxic in high levels.

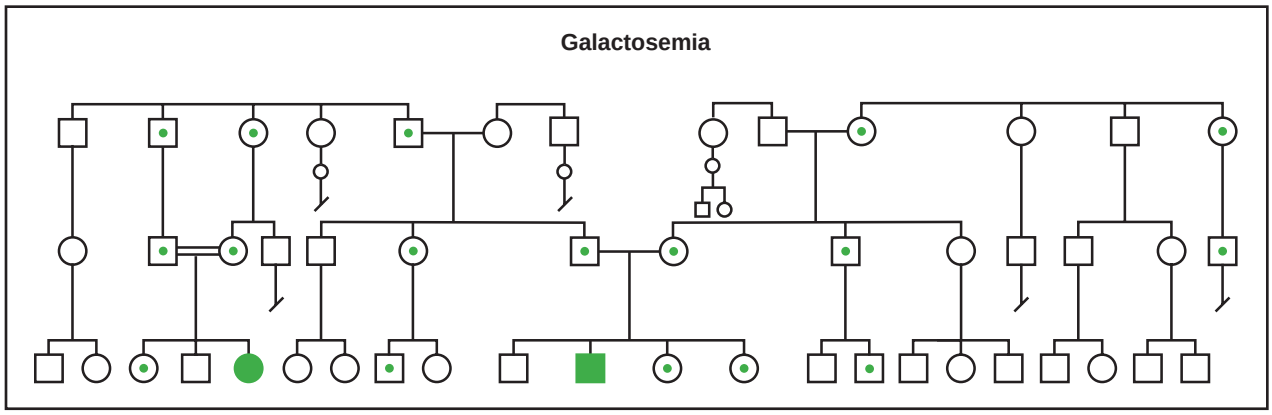
Glucose—One of the two simple sugars, together with galactose, that makes up the protein, lactose, found in milk. Glucose is the form of sugar that is usable by the body to generate energy.

Lactose—A sugar made up of of glucose and galactose. It is the primary sugar in milk.

Metabolic pathway—A sequence of chemical reactions that lead from some precursor to a product, where the product of each step in the series is the starting material for the next step.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Recessive trait—An inherited trait or characteristic that is outwardly obvious only when two copies of the gene for that trait are present.



(Gale Group)

In addition, galactosemic babies who are refusing milk or vomiting will not have elevated levels of galactose or galactose phosphate, and their condition will not be detected by the initial screen. Any baby with symptoms of galactosemia (for example, vomiting) should be given enzyme tests.

Treatment and management

Galactosemia I and II are treated by removing galactose from the diet. Since galactose is a break-down product of lactose, the primary sugar constituent of milk, this means all milk and foods containing milk products must be totally eliminated. Other foods like legumes, organ meats, and processed meats also contain considerable galactose and must be avoided. Pills that use lactose as a filler must also be avoided. Soy-based and casein hydrolysate-based formulas are recommended for infants with galactosemia.

Treatment of the severe form of galactosemia III with a galactose-restricted diet has been tried, but this disorder is so rare that the long-term effects of this treatment are unknown.

Prognosis

Early detection in the newborn period is the key to controlling symptoms. Long-term effects in untreated babies include severe mental retardation, cirrhosis of the liver, and death. About 75% of the untreated babies die within the first two weeks of life. On the other hand, with treatment, a significant proportion of people with galactosemia I can lead nearly normal lives, although speech defects, learning disabilities, and behavioral problems are common. In addition, cataracts due to galactosemia II can be completely prevented by a galactose-free diet.

Prevention

Since most people are unaware that they are carriers of a gene mutation causing galactosemia, the disease is usually detected on a newborn screening test. For couples with a previous child with galactosemia, prenatal diagnosis is available to determine whether a pregnancy is similarly affected. Families who have a child diagnosed with galactosemia can have DNA testing, which would enable other more distant relatives to determine their carrier status. Prospective parents can then use that information to conduct family planning or to prepare for a child with special circumstances. Children born with galactosemia should be put on a special diet right away to reduce the symptoms and complications of the disease.

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Association for Neuro-Metabolic Disorders. 5223 Brookfield Lane, Sylvania, OH 43560. (419) 885-1497.

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Amy Vance, MS, CGC

Galactosialidosis *see* **Neuraminidase deficiency with beta-galactosidase deficiency**

GALK deficiency *see* **Galactokinase deficiency**

Gangliosidosis-GM1 *see* **GM1 gangliosidosis**

Gardner syndrome *see* **Familial adenomatous polyposis**

Gastric cancer *see* **Stomach cancer**

Gaucher disease

Definition

Gaucher disease is a rare genetic disorder that results in accumulation of fatty molecules called cerebrosides. It can have serious effects on numerous body organs including the liver, spleen, bones, and central nervous system. Treatments based on molecular biology are becoming available, but are very expensive.

Description

Gaucher disease was first described by the French physician Philippe Gaucher in 1882. It is the most common of a class of diseases called lysosomal storage diseases, each of which is characterized by the accumulation of a specific chemical substance (a different substance depending on the exact disease). Gaucher disease is characterized by a wide array of different symptoms and the severity of the disease ranges from undetectable to lethal.

Three forms of the disease are recognized: Types I, II, and III. Type I is by far the most common and shows the mildest symptoms. It is non-neuronopathic, meaning that the nervous system is not attacked. The onset of Type I can occur at any age in childhood or adult life, with the average age of onset at about 21 years. Some affected individuals have no symptoms throughout adult life. Type II, the infantile form, accounts for less than 1% of patients with Gaucher disease. It is neuronopathic (attacks the nervous system); nervous system effects are severe, and victims often die within the first year of life. Type III most often has its onset during childhood and has some of the features of both the adult and infantile forms. This affects less than 5% of persons with Gaucher disease.

Gaucher disease is caused by the absence, or near absence, of activity of an enzyme called glucocerebrosidase (GC). The normal action of GC is to break down a common molecule called glucocerebroside. If not broken down, glucocerebroside accumulates in certain cells to levels that can cause damage, especially in the spleen, liver, and bone. The common link among these organs is that they house a cell type called a macrophage. A macrophage is a large cell that surrounds and consumes a foreign substance (such as bacteria) in the body. The cellular structures in which glucocerebroside accumulates are called lysosomes.

Genetic profile

Lack of the GC enzyme is caused by a mutation in the glucocerebrosidase **gene**. The gene is located on chromosome 1. As of 2000, there have been over 100 mutations described in this gene that causes Gaucher disease. Gaucher disease is inherited in an autosomal recessive pattern. This means that two defective gene copies must be inherited, one from each parent, for the disease to manifest itself. Persons with only one **gene mutation** are carriers for the disorder. A person who is a carrier for Gaucher disease does not have any symptoms and does not know he or she is a carrier unless he or she has had specific testing. When both parents are carriers for Gaucher disease, there is a one in four chance (25%) in each pregnancy for a child to have Gaucher disease. There is a two in three chance that a healthy sibling of an affected child is a carrier.

Demographics

The three forms of Gaucher disease also differ in their population genetics. Type I is most common in persons of eastern European (Ashkenazi) Jewish descent. Among this population, the disease occurs at a rate of one in 450 live births and about one in 10 to 15 persons are carriers, making it the most common genetic disease affecting Jewish people. The other two types are equally frequent in all ethnic groups. Type II occurs at a rate of one in 100,000 live births, while Type III is estimated to occur in one in 50,000 live births.

Signs and symptoms

The results of Gaucher disease are widespread in the body and include excessive growth of the liver and spleen (hepatosplenomegaly), weakening of bones, and, in acute cases, severe nervous system damage. Many patients experience “bone crises,” which are episodes of extreme pain in their bones.

There is a wide array of other problems that occur with Gaucher disease, such as anemia (fewer than normal red blood cells). Just how these other symptoms are

KEY TERMS

Cerebrosides—Fatty carbohydrates that occur in the brain and nervous system.

Enzymatic replacement therapy—A treatment method used to replace missing enzymes. It is possible to synthesize enzymes and then inject them intravenously into patients.

Glucocerebroside—A cerebroside that contains glucose in the molecule.

caused is not known, nor is it known why some patients have very mild disease and others have much more significant problems. Even identical twins with the disease can have differing symptoms.

Diagnosis

Diagnosis of Gaucher disease, based initially on the symptoms described above, can be confirmed by microscopic, enzymatic, and molecular tests. Biopsy (surgical removal of tissue from a problem area) of tissue is helpful for microscopic diagnosis. When biopsy tissue is examined under the microscope, cells will appear swollen and will show characteristic features of the cytoplasm (part of the cell body along with the nucleus) and nucleus. Enzyme tests will show deficiency (<30% of normal levels) of the enzyme GC. Molecular analysis of **DNA** samples looking at four of the more common mutations will show defects in the gene for GC in 95% of Ashkenazi Jewish individuals and in 75% of non-Jewish people. Diagnosis can be performed prenatally (before birth) if the parents' mutations are known using **amniocentesis** or chorionic villus sampling.

Diagnosis as to which of the three types of Gaucher disease an individual has is based on the symptoms, rather than on test results.

Treatment and management

Until the 1990s, only supportive therapy could be offered. Analgesics are used to control pain. Orthopedic treatment is used for bone fractures. In some cases, surgical removal of the spleen may be necessary. Several treatments for anemia have been used, including vitamin and iron supplements, blood transfusions, and bone marrow transplants.

The newest form of treatment for Gaucher disease is enzyme replacement therapy, in which GC can be administered intravenously. The enzyme can be prepared either by purification from placentas (alglucerase) or by recombinant DNA manufacturing techniques (imiglucerase). Either way, the cost of treatment ranges from $100,000 to $400,000 per year, which can prevent many from obtaining treatment.

Enzyme replacement is effective at reducing most Gaucher symptoms. The notable exception is neurologic damage in Type II disease, which remains unimproved by this treatment. This treatment is not recommended for individuals who are asymptomatic. As of 2000, the efficacy for the treatment of Type III Gaucher disease is not known. Many questions remain about enzyme replacement therapy in regard to dosage, and method and frequency of administration. The treatment program should be individualized for each patient.

Prognosis

A patient's expected lifespan varies greatly with the type of Gaucher disease. Infants with Type II disease have a life span of one to four years. Patients with Types I and III of the disease have highly variable outcomes, with some patients dying in childhood and others living full lives. Little is known about the reasons for this variability.

Prevention

Genetic counseling is advised for individuals with Gaucher disease and for their relatives to accurately assess risk and discuss testing options. For couples who previously had a child with Gaucher or in situations where both parents are carriers for known Gaucher mutations, prenatal diagnosis is available to determine whether a pregnancy is affected. Families in which a person has been diagnosed with Gaucher disease can have DNA testing, which enables other relatives to determine their carrier status. Prospective parents can then use that information to conduct family planning or to prepare for a child who may have special circumstances.

Families in which both parents are known to be a carrier of a mutation for Gaucher disease could consider preimplantation genetic diagnosis. This relatively new procedure can select an embryo without both Gaucher disease mutations prior to implantation of the embryo into the uterus. This technique is only available at selected genetics centers.

As of 2000, population screening for Gaucher disease is not standard care.

Resources

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ORGANIZATIONS

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

Children's Gaucher Research Fund. PO Box 2123, Granite Bay, CA 95746-2123. (916) 797-3700. Fax: (916) 797-3707. <http://www.childrensgaucher.org>.

National Gaucher Foundation. 11140 Rockville Pike, Suite 350, Rockville, MD 20852-3106. (800) 925-8885. <http://www.gaucherdisease.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Amy Vance, MS, CGC

Gene

A gene is the fundamental physical and functional unit of heredity. It is an individual element of an organism's genome and determines a trait or characteristic by regulating biochemical structure or metabolic process.

Genes are segments of nucleic acid, consisting of a specific sequence and number of the chemical units of nucleic acids, the nucleotides. In most organisms the nucleic acid is deoxyribonucleic acid (**DNA**), although in retroviruses the genetic material is composed of ribonucleic acid (**RNA**). Some genes in a cell are active more or less all the time, which means that they are continuously transcribed and provide a constant supply of their protein product. These are the "housekeeping" genes that are always needed for basic cellular reactions. Others may be rendered active or inactive depending on the needs and functions of the organism under particular conditions. The signal that masks or unmasks a gene can come from outside the cell, for example, from a steroid hormone or a nutrient, or it can come from within the cell itself as a result of the activity of other genes. In both cases, regulatory substances can bind to the specific DNA sequences of the target genes to control the synthesis of transcripts.

In a paper published in 1865, Gregor Mendel (1823–1884) advanced a theory of **inheritance** dependent on material elements that segregate independently from each other in sex cells. Before Mendel's findings, inherited traits were thought to be passed on through a blending of the mother and father's characteristics, much like a blending of two liquids. The term "gene" was coined later by the Danish botanist Wilhelm Johannsen (1857–1927), to replace the variety of terms used up until then to describe hereditary factors. His definition of the gene led him to distinguish between genotype (an organism's genetic makeup) and phenotype (an organism's appearance). Before the chemical and physical nature of genes were discovered they were defined on the basis of phenotypic expression and algebraic symbols were used to record their distribution and segregation. Because sexually reproducing, eukaryotic organisms possess two copies of an inherited factor (or gene), one acquired from each parent, the genotype of an individual for a particular trait is expressed by a pair of letters or symbols. Each of the alternative forms of a gene is also known as alleles. Dominant and recessive alleles are denoted by the use of higher and lower case letters. It can be predicted mathematically, for example, that a single allele pair will always segregate to give a genotype ratio 1AA:2Aa:1aa, and the phenotype ratio 2A:1aa (where A represents both AA and Aa since these cannot be distinguished phenotypically if dominance is complete).

The molecular structure and activity of genes can be modified by mutations and the smallest mutational unit is now known to be a single pair of nucleotides, also known as a muton. To indicate that a gene is functionally normal, it is assigned a plus (+) sign, whereas a damaged or mutated gene is indicated by a minus (−) sign. A wild type *Escherichia coli* able to synthesize its own arginine would thus be symbolized as *arg*+, and strains that have lost this ability by mutation of one of the genes for arginine utilization would be *arg*−. Such strains, known as arginine auxotrophs, would not be able to grow without a supplement of arginine. At this level of definition, the plus or minus actually refer to an operon rather than a single gene, and finer genetic analysis can be used to reveal the exact location of the mutated gene.

The use of mutations in studying genes is well-illustrated in a traditional genetic test called the "cis-trans test" which also gave the gene the alternative name, cistron. This is a complemetntation test that can be used to determine whether two different mutations (m^1 and m^2) occur

in the same functional unit, i.e., within the same gene or cistron. It demonstrates well how genes can be defined phenomenologically and has been performed successfully in microrganisms such as yeasts. It works on the principle that pairs of homologous **chromosomes** containing similar genes can complement their action. Two types of heterozygotes of the test organism are prepared. Heterozygotes are organisms with different alleles in the two homologous chromosomes, each of which was inherited from one parent. One heterozygote contains the mutations under investigation within the same chromosome, that is in the cis-configuration, which is symbolically designated $++/m^1m^2$ (m^1 and m^2 are the two mutations under investigation and the symbol "+" indicates the same position on the homologous chromosome in the unmutated, wild type state). The second mutant is constructed to contain the mutations in such a way that one appears on each of the homologous chromosomes. This is called the trans-configuration and is designated, for example, by $m^2+/+m^1$. If two recessive mutations are present in the same cistron, the heterozygous trans-configuration displays the mutant phenotype, whereas the cis-configuration displays the normal, wild type phenotype. This is because in the cis-configuration, there is one completely functional, unmutated, cistron (++) within the system that masks the two mutations on the other chromosome and allows for the expression of the wild type phenotype. If one or both mutations are dominant, and the cis- and trans-heterozygotes are phenotypically different, then both mutations must be present in the same cistron. Conversely, if the cis- and trans-heterozygotes are phenotypically identical, this is taken as evidence that the mutations are present in different cistrons.

In 1910, the American geneticist Thomas Hunt Morgan (1866–1945) began to uncover the relationship between genes and chromosomes. He discovered that genes were located on chromosomes and that they were arranged linearly and associated in linkage groups, with all the genes on one chromosome being linked. For example, the genes on the X and Y chromosomes are said to be sex-linked because the X and Y chromosomes determine the sex of the organisms, (in humans, X determines femaleness and Y determines maleness). Nonhomologous chromosomes possess different linkage groups, whereas homologous chromosomes have identical linkage groups in identical sequences. The distance between two genes of the same linkage group is the sum of the distances between all the intervening genes. A schematic representation of the linear arrangement of linked genes, with their relative distances of separation, is known as a genetic map. In the construction of such maps the frequency of recombination during crossing over is used as an index of the distance between two linked genes.

Advances in molecular genetics have allowed analysis of the structure and biochemistry of genes in greater detail. They are no longer the nebulous units described by Mendel purely in terms of their visible expression (phenotypic expression). It is now possible to understand their molecular structure and function in considerable detail. The biological role of genes is to carry, encode, or control information on the composition of proteins. The proteins, together with their timing of expression and amount of production, are possibly the most important determinants of the structure and physiology of organisms. Each structural gene is responsible for one specific protein or part of a protein and codes for a single polypeptide chain via messenger RNA (mRNA). Some genes code specifically for transfer RNA (tRNA) or ribosomal RNA (rRNA) and some are merely sequence that are recognized by regulatory proteins. The latter are termed regulator genes. In higher organisms, or eukaryotes, genes are organized in such a way that at one end there is a region to which various regulatory proteins can bind, for example, RNA polymerase during transcription, and at the opposite end there are sequences encoding the termination of transcription. In between lies the protein encoding sequence. In the genes of many eukaryotes, this sequence may be interrupted by intervening non-coding sequence segments called introns, which can range in number from one to many. Transcription of eukaryotic DNA produces pre-mRNA containing complementary sequences of both introns and the information carrying sections of the gene called exons. The pre-mRNA then undergoes post-transcriptional modification or processing in which the introns are excised and exons are spliced together, leaving the complete coding transcript of connected exons ready to code directly for the protein. When the central dogma of genetics was first established, a "one gene-one enzyme" hypothesis was proposed, but today it is more accurate to restate this as a one-to-one correspondence between a gene and the polypeptide for which it codes. This is because a number of proteins are now known to be constituted of multiple polypeptide subunits coded by different genes.

Judyth Sassoon, ARCS, PhD

Genetic mapping

The aim of genetic mapping is to determine the linear sequence of genes in genetic material. The mapping can be performed at several levels of detail (resolution) that fall into two broad types: traditional genetic or linkage mapping and more detailed, physical mapping.

Linkage mapping shows the relative rather than absolute positions of genes along a chromosome and is a technique that has been used since the early 1900s. Early geneticists determined that genes were found on **chromosomes**. They also reasoned that because the various forms of genes, or alleles, could be precisely exchanged during meiosis through crossovers between homologous chromosomes, the genes for specific characteristics must lie at precise points along each chromosome. It followed that the mapping of chromosomes could, therefore, be made from the observation of crossovers. Between 1912 and 1915, the American scientist Thomas Hunt Morgan (1866–1945) hypothesized that if genes were arranged linearly along chromosomes, then those genes lying closer together would be separated by crossovers less often than those lying further apart. Genes lying closer together would thus have a greater probability of being passed along as a unit. It follows that the percentage of crossovers would be proportional to the distance between two genes on a chromosome. The percentage crossover can be expressed as the number of crossovers between two genes in meiosis. One genetic map unit (m.u.) is defined as the distance between **gene** pairs for which one product out of 100 is recombinant (a product of crossover). S recombinant frequency (R.F.) of 0.01 (1%) is defined as 1 m.u., and a map unit is sometimes referred to as a centimorgan (cM) in honor of Thomas Hunt Morgan.

As an example of how linkage mapping might work, suppose two characteristics, A and B, show a 26% crossover. Assign 26 crossover units to the distance between these two genes. If a characteristic C turns out in breeding experiments to have 9% crossover with B and 17% crossover with A, it would then be located between A and B at a point 9 units from B and 17 units from A. Compiling the information from many such breeding experiments creates a chromosome map that indicates the relative positions of the genes that code for certain characteristics. Accordingly, the further apart any two genes are on the same chromosome, the greater the incidence of crossing over between them.

A linkage map is limited because recombination frequencies can be distorted relative to the physical distance between sites. As a result, the linkage map is not always the best possible representation of genetic material.

While linkage maps only indicate relative positions of genes, physical maps are more accurate and aim to show the actual number of nucleotides between each gene. Restriction maps are constructed by cleaving **DNA** into fragments with restriction enzymes. These enzymes recognize specific short DNA sequences and cut the duplex. The distances between the sites of cleavage are then measured. The positions of the target restriction sites for these enzymes along the chromosome can be used as DNA markers. Restriction sites generally exist in the same positions on homologous chromosomes so the positions of these target sites can be used rather like milestones along a road and can act as reference points for locating significant features in the chromosome.

A map of the positions of restriction sites can be made for a localized region of a chromosome. It is made by comparing the sizes of single enzyme breakages (digests) of the region of interest with double digests of the same region. This means that two different restriction enzymes are applied, one to each of two separate chromosome extracts of the region of interest, and subsequently the two enzymes are used together in a third digestion with the chromosome extract. The chromosome fragments resulting from the three digestions are then subjected to a biochemical procedure known as gel electrophoresis, which separates them and gives an estimation of their size. Comparison of the sizes of the chromosome fragments resulting from single and double restriction enzyme digestions allows for an approximate location of the target restriction sites. Thus, such maps represent linear sequences of restriction sites. As this procedure determines the sizes of digested chromosome fragments, the distances between sites in terms of the length of DNA can be calculated, because the size of a fragment estimated from an electrophoresis experiment is proportional to the number of base pairs in that fragment.

A restriction map does not intrinsically identify sites of genetic interest. For it to be of practical use, mutations have to be characterized in terms of their effects upon the restriction sites. In the 1980s, it was shown how restriction fragment length polymorphisms (RFLPs) could be used to map human disease genes. RFLPs are inherited by Mendelian segregation and are distributed in populations as classical examples of common genetic polymorphisms. If such a DNA variant is located close to a defective gene (which cannot be tested directly), the DNA variant can be used as a marker to detect the presence of the disease-causing gene. The prenatal examination of DNA for particular enzyme sites associated with certain hereditary diseases has proved to be an important method of diagnosis. Clinically useful polymorphic restriction enzyme sites have been detected within the Beta-like globin gene cluster. For example, the absence of a recognition site for the restriction enzyme HpaI is frequently associated with the allele for sickle-cell anemia, and this association has been useful in prenatal diagnosis of this disease.

The ultimate genetic map is the complete nucleotide sequence of the DNA in the whole chromosome complement, or genome, of an organism. Today, several completed genome maps already exist. Simple prokaryotic organisms, e.g., bacteria, with their relatively small

chromosomes of one to two million base pairs were the first to be mapped. Later, eukaryotic organisms such as the yeast, *Saccharomyces cerevisiae*, and the nematode worm, *Caenorhabditis elegans*, were mapped. In 2000, the **Human Genome Project** produced the first draft of the human genome. The project adopted two methods for mapping the three billion nucleotides. The earlier approach was a "clone by clone" method. In this, the entire genome was cut into fragments up to several thousand base pairs long, and inserted into synthetic chromosomes known as bacterial artificial chromosomes (BACs). The subsequent mapping step involved positioning the BACs on the genome's chromosomes by looking for distinctive marker sequences called sequence tagged sites (STSs), whose location had already been pinpointed. Clones of the BACs are then broken into smaller fragments in a process known as shotgun cloning. Each small fragment was then sequenced and computer algorithms, that recognize matching sequence information from overlapping fragments, were used to reconstruct the complete sequence inserted into each BAC. It was later argued that the first mapping step was unnecessary and that the algorithms used to reassemble the shotgunned DNA fragments could be applied to cloned random fragments taken directly from the whole genome. In this whole genome shotgun strategy, fragments were first assembled by algorithms into larger scaffolds and the correct position of these scaffolds on the genome was worked out by STSs. The latter method speeded up the whole procedure considerably and is currently being used to sequence genomes from other organisms.

Judyth Sassoon, ARCS, PhD

Gene mutations

In a strict sense, mutations are changes in genes not caused by genetic recombination. A change in the base sequence of **DNA**, for example, represents a mutational change. Spontaneous mutations are mutations that occur at a given frequency without the need for an inducing agent of change (mutagenic agent). The term mutation is also used in a less technical sense to describe changes in the human genome (i.e., evolution) that result from a broad spectrum of processes that act to increase or decrease genetic variation within a population.

By definition, a **gene** is a hereditary unit that carries information used to construct proteins via the processes of transcription and translation. The human **gene pool** is the set of all genes carried within the human population. Genetic changes, including mutations, can be beneficial, neutral or deleterious. In general, mutations, along with recombination and gene flow, act to increase genetic variation (i.e., the number of types of genes or alleles) within the human species.

The term mutation was originally used by Dutch botanist Hugo De Vries (1848–1935) to describe rapid changes in phenotype from one generation to the next. Subsequently, scientists used the term mutation to describe long-term, multi-generational, and heritable physical changes to genes.

Mutations generally occur via chromosomal mutations, point mutations, frame shifts, and breakdowns in DNA repair mechanisms. Chromosomal mutations include translocations, inversions, deletions and chromosome non-disjunction. Essentially there are five types of genetic rearrangements: deletions, duplications, inversions, translocations, and transposition.

Mutational deletions physically remove portions of genes (e.g., a portion of the DNA comprising the gene). Deletional mutations range from the single base point mutations to mutations that can span many functional genes. Chemical and radioactive agents account for the majority of induced point mutations. Scientists currently argue that most cancers and other degenerative diseases result from acquired genetic mutations due to environmental exposure, and not as an outcome of inherited traits. Chemicals capable of inducing genetic mutation (i.e., chemical mutagenesis or genotoxic compounds) are present a wide variety of natural and man-made products.

Point mutations may be nonsense mutations leading to the early termination of protein synthesis, missense mutations (a mutation that results an a substitution of one amino acid for another in a protein), or silent mutations that cause no detectable change. Accordingly, the effects of point mutational changes range from 100% lethality (all individuals die, usually early in fetal development) to no observable (phenotypic) change.

Duplications result in multiple copies of genes, and can occur as a result of unequal crossover or chromosome breaks. In addition, because some alteration of DNA is inevitable in the replication process, any mutation that hinders DNA repair mechanism will also increase the chance that a mutation will go uncorrected. Duplications also manifest a range of deleterious effects.

Inversions, which are changes in the orientation of gene bearing chromosomal regions, may cause deleterious effects if the inversion breaks through a gene critical for a particular protein or enzyme.

Translocations occur when one a portion of one chromosome becomes linked to a non-homologous chromosome (a chromosome outside its normal pairing) or

when portions of non-homologous **chromosomes** make a reciprocal exchange. Once again, the effect of such genetic change is a result of whether such translocations physically or functionally alter vital genes.

Recombination involves the reassortment of genes through new chromosome combinations. Recombination occurs via an exchange of DNA between homologous chromosomes (crossing over) during meiosis. Recombination also includes linkage disequilibrium. With linkage disequilibrium,variations of the same gene (alleles) occur in different combinations in the gametes (sexual reproductive cells) than should occur according to the rules of probability.

Gene flow occurs when individuals change their local genetic group by moving from one place to another. These migrations allow the introduction of new variations of the same gene (alleles) when they mate and produce offspring with members of their new group. In effect, gene flow acts to increase the gene pool in the new group. Because genes are usually carried by many members of a large population that has undergone random mating for several generations, random migrations of individuals away from the population or group usually do not significantly decrease the gene pool of the group left behind.

In contrast to mechanisms that operate to increase genetic variation, there are fewer mechanisms that operate to decrease genetic variation. Mechanisms that decrease genetic variation include genetic drift and natural selection.

Genetic drift results form the changes in the numbers of different forms of a gene (allelic frequency) that result from sexual reproduction. Genetic drift can occur as a result of random mating (random genetic drift) or be profoundly affected by geographical barriers, catastrophic events (e.g., natural disasters or wars that significantly affect the reproductive availability of selected members of a population) and other political-social factors.

Natural selection is based upon the differences in the viability and reproductive success of different genotypes with a population (differential reproductive success). Natural selection can only act on those differences in genotype that appear as visible (phenotypic) differences that affect the ability to attract a mate and produce viable offspring that are, in turn, able to live, mate and continue the species. The term evolutionary fitness describes the success of an entity in reproducing (i.e., contributing alleles to the next generation).

There are three basic types of natural selection. With directional selection, an extreme phenotype is favored (high or low body fat). Stabilizing selection occurs when an intermediate phenotype is fittest (e.g., body fat content is neither too high nor low) and for this reason it is often referred to a normalizing selection. Disruptive selection occurs when two extreme phenotypes are fitter than an intermediate phenotype. In studying changes in the human genome, the operation of natural evolutionary mechanisms is complicated by geographic, ethnic, religious, and social groups and customs. Accordingly, the effects of various evolution mechanisms on human populations are not as easy to predict. Increasingly sophisticated statistical studies are carried out by population geneticists to characterize changes in the human genome.

Polydactyly, which results in extra fingers or toes, is one type of genetic mutation. *(Custom Medical Stock Photo, Inc.)*

K. Lee Lerner

Gene pool

Definition

The term gene pool refers to the total sum of genetic information present in a population at any given time. A gene pool can be assigned to any set group or population. This is true for plants, animals, and humans alike. Each gene pool contains all of the inherited information for all of the traits of the members of the population.

Genetic information

Genetic information, in the form of deoxyribonucleic acid (**DNA**), is passed down from generation to generation. DNA tells a person's body how to work and how to grow. It provides instructions that assign features to each individual, such as giving one person brown hair and another person blonde hair, and one person brown eyes and another person green eyes.

KEY TERMS

Allele—One of two or more alternate forms of a gene.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genome—A term used to describe a complete representation of all of the genes in a species.

DNA is much like a linear string, with individual segments along the string known as genes. Genes provide the specific directions for the body. Each gene is a segment of DNA, and sequencing of the four base molecules of DNA create the gene. Variations in the sequence account for variations in genes. A gene is the equivalent of an allele, and each particular gene is found on the same chromosome in each individual. The long, linear strings of DNA are arranged into smaller packages known as **chromosomes**. In general, there are 46 chromosomes in each cell of a person's body. The 46 chromosomes can be matched into 23 pairs. One of each pair is inherited from the mother's egg and one of each pair is inherited from the father's sperm. Most animals, including humans, contain two copies of each chromosome and likewise two copies of each gene. Each individual receives one allele from each parent because they receive one of each of the 23 chromosomes from each parent.

Although each person has 46 chromosomes, the DNA that makes up those chromosomes is slightly different from individual to individual. It is this variation within specific genes that gives the diversity observed throughout populations around the world.

Alleles

Different versions of the same gene are referred to as alleles. Blood types are examples of alleles. In humans there are several different blood types, including A, B, O, and AB. These arise by various combinations of the three blood-type alleles; the A-allele, the B-allele, and the O-allele. The specific blood type a person has depends on the exact blood type alleles they inherited from their parents. For example, a person may inherit two O-alleles, in which case they would have type O blood, or they may inherit an A- and a B-allele, in which case they would have type AB blood, and so on.

Population genetics

Population genetics is the study of genetic variation within a population. This includes the subtle changes in DNA sequences and the frequencies of these different forms. Changes within the DNA sequences may arise through several pathways. Mechanisms commonly studied by population geneticists include mutation, natural selection, and genetic drift.

Mutations are changes within the DNA sequence that alter the original directions encoded within DNA. Mutation may result from damage to DNA, or a mistake in the replication of DNA resulting in a sequence change. The majority of mutations arise by chance, although some may be caused by environmental factors, such as toxins that penetrate the cells of the body and attack the DNA. Natural selection is the difference in mortality (death rates) and fertility (birth rates) between different genetic types. The interplay of the expressed phenotype and the environment influences natural selection. If the phenotype is favorable, the individual survives and perpetuates his or her genetic profile in the gene pool. Genetic drift is a process by which the frequencies of specific alleles change, by chance, within a population.

Each gene pool accounts for all of the alleles for all of the traits of the members of a population. Within a population, different alleles will occur at different frequencies. For instance, approximately 44% of the population has type O blood, 42% of the population has type A blood, 10% of the population has type B blood, and 4% of the population has type AB blood. The percentages of each blood type are directly related to the frequency of each blood type allele. The more frequent the A-allele, the more frequent type A blood would be seen in the population.

The gene frequency of an allele is equal to the number of times the allele occurs compared to the total number of alleles for that trait.

Gene frequency equals the number of a specific type of allele, or the total number of alleles in the gene pool

DNA changes and genetic disorders

Genetic disorders are caused by changes in the DNA sequence. In general, there is a non-disease causing

Three generations of female twins. *(Phototake)*

allele and a disease-causing allele. Some genetic disorders arise by sporadic mutations in the DNA sequence. Others are inherited from one or both of the parents.

There are several different **inheritance** patterns associated with genetic disorders. Autosomal dominant and autosomal recessive are two of the most common. Chromosomes come in pairs, one from the egg and one from the sperm. Autosomal dominant disorders require that a person inherit only one disease-causing allele in order to be affected. Even though the corresponding gene on the other chromosome in the pair may be the non-disease-causing allele, having one disease-causing allele is enough to cause the disorder to be present. Autosomal recessive disorders require that a person inherit two disease-causing alleles, one on each chromosome of the pair, for the individual to be affected. If a person inherits only one disease-causing allele of a recessive disorder they are called a carrier. Carriers are not affected by disease; however, they carry the possibility of passing that disease on to a future child.

Hardy-Weinberg equilibrium

The frequency of disease-causing and non-disease-causing alleles along with the frequency of affected individuals, carriers, and unaffected individuals are related within a mathematical equation known as the Hardy-Weinberg equation.

The equation itself is written as $p^2+2pq+q^2=1$. For autosomal recessive disorders, p^2 represents the people within the population that have two non-disease-causing alleles (unaffected), 2pq represents the people within the population with one disease-causing allele and one non-disease-causing allele (carriers), and q^2 represents the people within the population that have two disease-causing alleles (affected). Because the Hardy-Weinberg equation deals with allele frequencies, the equation $p + q = 1$ may also be used. In this case, p represents the frequency of the non-disease-causing allele within the population and q represents the frequency of the disease-causing allele within the population.

The Hardy-Weinberg equation is based on the work of Drs. Hardy and Weinberg. Independently, they suggested that there should exist an equilibrium, or balance, between different allele frequencies. They devised a list of conditions that must be true for this balance, known as the Hardy-Weinberg equilibrium, to occur. These include:

• no evolutionary forces acting upon the population

- the population is "infinitely" large (meaning it is so large that it may be assumed to be infinitely large)
- individuals have two copies of each gene
- there is random mating between individuals within the group
- the frequencies of the alleles are the same in both males and females
- generations are non-overlapping

The Hardy-Weinberg equation has several applications including use by population geneticists to study the characteristics of certain populations and use by genetic counselors to calculate recurrence risks for individual families affected by genetic disease.

The future

There are several projects underway at this time in an effort to further understand the gene pool, population genetics, and the human genome. The Human Genome Diversity Project (HGDP) is an international project that seeks to understand the diversity and unity of the entire human species.

The **Human Genome Project**, a separate venture from HGDP, made the news in 2000 when scientists announced they had elucidated a working draft of the human genome sequence.

Resources

WEBSITES

Bioethics and Human Population Genetics Research. <http://www.biol.tsukuba.ac.jp/~macer/PG.html>.

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Talk Origins. <http://www.talkorigins.org>.

Java O. Solis, MS

Gene therapy

Gene therapy is a rapidly growing field of medicine in which genes are introduced into the body to treat diseases. Genes control heredity and provide the basic biological code for determining a cell's specific functions. Gene therapy seeks to provide genes that correct or supplant the disease-controlling functions of cells that are not, in essence, doing their job. Somatic gene therapy introduces therapeutic genes at the tissue or cellular level to treat a specific individual. Germ-line gene therapy inserts genes into reproductive cells or possibly into embryos to correct genetic defects that could be passed on to future generations. Initially conceived as an approach for treating inherited diseases, like **cystic fibrosis** and Huntington's disease, the scope of potential gene therapies has grown to include treatments for cancers, arthritis, and infectious diseases. Although gene therapy testing in humans has advanced rapidly, many questions surround its use. For example, some scientists are concerned that the therapeutic genes themselves may cause disease. Others fear that germ-line gene therapy may be used to control human development in ways not connected with disease, like intelligence or appearance.

The biological basis of gene therapy

Gene therapy has grown out of the science of genetics or how heredity works. Scientists know that life begins in a cell, the basic building block of all multicellular organisms. Humans, for instance, are made up of trillions of cells, each performing a specific function. Within the cell's nucleus (the center part of a cell that regulates its chemical functions) are pairs of **chromosomes**. These threadlike structures are made up of a single molecule of **DNA** (deoxyribonucleic acid), which carries the blueprint of life in the form of codes, or genes, that determine inherited characteristics.

A DNA molecule looks like two ladders with one of the sides taken off both and then twisted around each other. The rungs of these ladders meet (resulting in a spiral staircase-like structure) and are called base pairs. Base pairs are made up of nitrogen molecules and arranged in specific sequences. Millions of these base pairs, or sequences, can make up a single gene, specifically defined as a segment of the chromosome and DNA that contains certain hereditary information. The gene, or combination of genes formed by these base pairs ultimately direct an organism's growth and characteristics through the production of certain chemicals, primarily proteins, which carry out most of the body's chemical functions and biological reactions.

Scientists have long known that alterations in genes present within cells can cause inherited diseases like cystic fibrosis, sickle-cell anemia, and **hemophilia**. Similarly, errors in the total number of chromosomes can cause conditions such as **Down syndrome** or **Turner syndrome**. As the study of genetics advanced, however, scientists learned that an altered genetic sequence can also make people more susceptible to diseases, like ather-

KEY TERMS

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Clinical trial—The testing of a drug or some other type of therapy in a specific population of patients.

Clone—A cell or organism derived through asexual (without sex) reproduction containing the identical genetic information of the parent cell or organism.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Eugenics—A social movement in which the population of a society, country, or the world is to be improved by controlling the passing on of hereditary information through mating.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Gene transcription—The process by which genetic information is copied from DNA to RNA, resulting in a specific protein formation.

Genetic engineering—The manipulation of genetic material to produce specific results in an organism.

Genetics—The study of hereditary traits passed on through the genes.

Germ-line gene therapy—The introduction of genes into reproductive cells or embryos to correct inherited genetic defects that can cause disease.

Liposome—Fat molecule made up of layers of lipids.

Macromolecules—A large molecule composed of thousands of atoms.

Nitrogen—A gaseous element that makes up the base pairs in DNA.

Nucleus—The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Somatic gene therapy—The introduction of genes into tissue or cells to treat a genetic related disease in an individual.

Vectors—Something used to transport genetic information to a cell.

osclerosis, **cancer**, and even **schizophrenia**. These diseases have a genetic component, but are also influenced by environmental factors (such as diet and lifestyle). The objective of gene therapy is to treat diseases by introducing functional genes into the body to alter the cells involved in the disease process by either replacing missing genes or providing copies of functioning genes to replace nonfunctioning ones. The inserted genes can be naturally occurring genes that produce the desired effect or may be genetically engineered (or altered) genes.

Scientists have known how to manipulate a gene's structure in the laboratory since the early 1970s through a process called gene splicing. The process involves removing a fragment of DNA containing the specific genetic sequence desired then inserting it into the DNA of another gene. The resultant product is called recombinant DNA and the process is genetic engineering.

There are basically two types of gene therapy. Germline gene therapy introduces genes into reproductive cells (sperm and eggs) or someday possibly into embryos in hopes of correcting genetic abnormalities that could be passed on to future generations. Most of the current work in applying gene therapy, however, has been in the realm of somatic gene therapy. In this type of gene therapy, therapeutic genes are inserted into tissue or cells to produce a naturally occurring protein or substance that is lacking or not functioning correctly in an individual patient.

Viral vectors

In both types of therapy, scientists need something to transport either the entire gene or a recombinant DNA to the cell's nucleus, where the chromosomes and DNA reside. In essence, vectors are molecular delivery trucks. One of the first and most popular vectors developed were viruses because they invade cells as part of the natural infection process. Viruses have the potential to be excellent vectors because they have a specific relationship with the host in that they colonize certain cell types and tissues in specific organs. As a result, vectors are chosen according to their attraction to certain cells and areas of the body.

One of the first vectors used was the retrovirus. Because these viruses are easily cloned (artificially reproduced) in the laboratory, scientists have studied them extensively and learned a great deal about their biological action. They have also learned how to remove the genetic information which governs viral replication, thus reducing the chances of infection.

Retroviruses work best in actively dividing cells, but cells in the body are relatively stable and do not divide often. As a result, these cells are used primarily for *ex vivo* (outside the body) manipulation. First, the cells are removed from the patient's body, and the virus, or vector, carrying the gene is inserted into them. Next, the cells are placed into a nutrient culture where they grow and replicate. Once enough cells are gathered, they are returned to the body, usually by injection into the blood stream. Theoretically, as long as these cells survive, they will provide the desired therapy.

Another class of viruses, called the adenoviruses, may also prove to be good gene vectors. These viruses can effectively infect nondividing cells in the body, where the desired gene product is then expressed naturally. In addition to being a more efficient approach to gene transportation, these viruses, which cause respiratory infections, are more easily purified and made stable than retroviruses, resulting in less chance of an unwanted viral infection. However, these viruses live for several days in the body, and some concern surrounds the possibility of infecting others with the viruses through sneezing or coughing. Other viral vectors include influenza viruses, Sindbis virus, and a herpes virus that infects nerve cells.

Scientists have also delved into nonviral vectors. These vectors rely on the natural biological process in which cells uptake (or gather) macromolecules. One approach is to use liposomes, globules of fat produced by the body and taken up by cells. Scientists are also investigating the introduction of raw recombinant DNA by injecting it into the bloodstream or placing it on microscopic beads of gold shot into the skin with a "gene-gun." Another possible vector under development is based on dendrimer molecules. A class of polymers (naturally occurring or artificial substances that have a high molecular weight and formed by smaller molecules of the same or similar substances), is "constructed" in the laboratory by combining these smaller molecules. They have been used in manufacturing Styrofoam, polyethylene cartons, and Plexiglass. In the laboratory, dendrimers have shown the ability to transport genetic material into human cells. They can also be designed to form an affinity for particular cell membranes by attaching to certain sugars and protein groups.

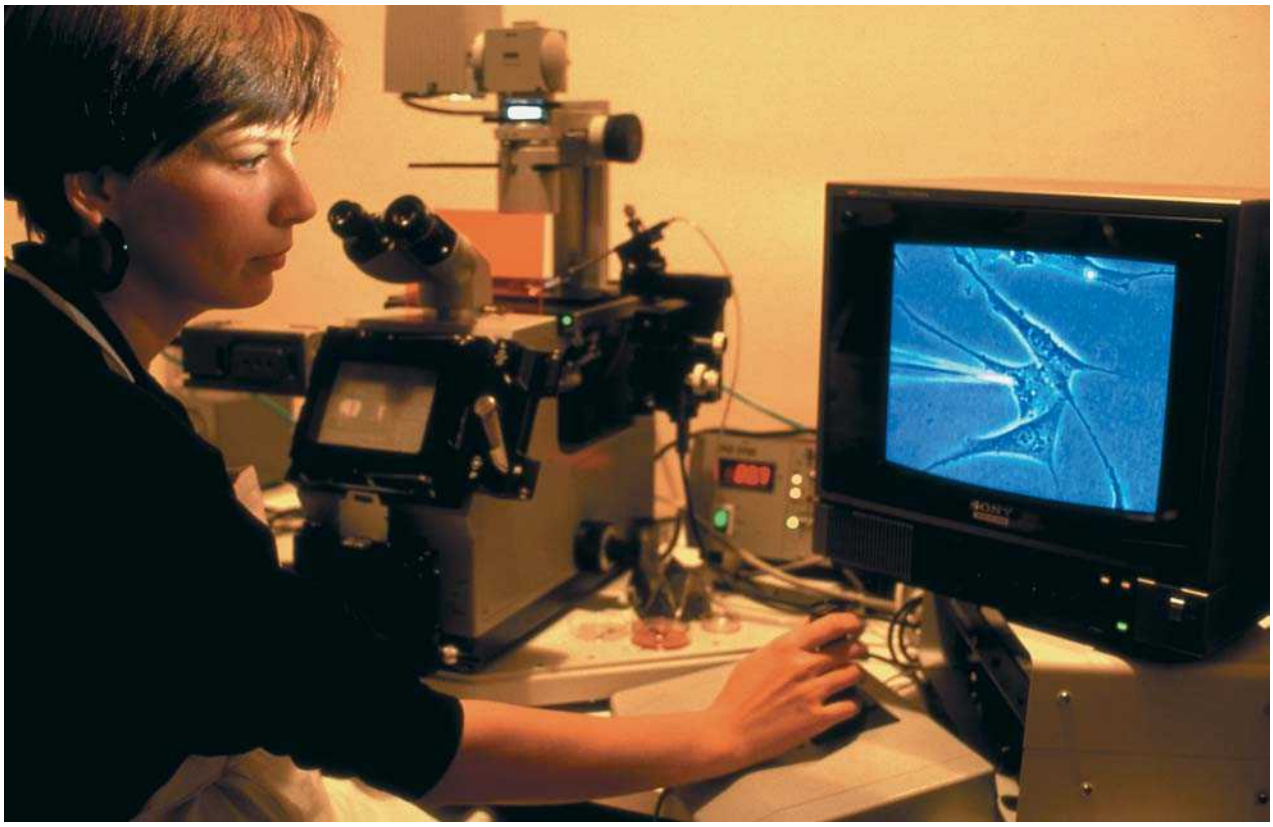
The history of gene therapy

In the early 1970s, scientists proposed "gene surgery" for treating inherited diseases caused by faulty genes. The idea was to take out the disease-causing gene and surgically implant a gene that functioned properly. Although sound in theory, scientists, then and now, lack the biological knowledge or technical expertise needed to perform such a precise surgery in the human body.

However, in 1983, a group of scientists from Baylor College of Medicine in Houston, Texas, proposed that gene therapy could one day be a viable approach for treating Lesch-Nyhan disease, a rare neurological disorder. The scientists conducted experiments in which an enzyme-producing gene (a specific type of protein) for correcting the disease was injected into a group of cells for replication. The scientists theorized the cells could then be injected into people with Lesch-Nyhan disease, thus correcting the genetic defect that caused the disease.

As the science of genetics advanced throughout the 1980s, gene therapy gained an established foothold in the minds of medical scientists as a promising approach to treatments for specific diseases. One of the major reasons for the growth of gene therapy was scientists' increasing ability to identify the specific genetic malfunctions that caused inherited diseases. Interest grew as further studies of DNA and chromosomes (where genes reside) showed that specific genetic abnormalities in one or more genes occurred in successive generations of certain family members who suffered from diseases like intestinal cancer, manic-depression, Alzheimer's disease, heart disease, diabetes, and many more. Although the genes may not be the only cause of the disease in all cases, they may make certain individuals more susceptible to developing the disease because of environmental influences, like smoking, pollution, and stress. In fact, some scientists theorize that all diseases may have a genetic component.

On September 14, 1990, a four-year-old girl with a genetic disorder that prevented her body from produc-



Geneticist performing DNA microinjection technique. The monitor shows the micropipette injecting DNA into a cell. *(Photo Researchers, Inc.)*

ing a crucial enzyme became the first person to undergo gene therapy in the United States. Because her body could not produce adenosine deaminase (ADA), she had a weakened immune system, making her extremely susceptible to severe, life-threatening infections. W. French Anderson and colleagues at the National Institutes of Health's Clinical Center in Bethesda, Maryland, took white blood cells (which are crucial to proper immune system functioning) from the girl, inserted ADA producing genes into them, and then transfused the cells back into the patient. Although the young girl continued to show an increased ability to produce ADA, debate arose as to whether the improvement resulted from the gene therapy or from an additional drug treatment she received.

Nevertheless, a new era of gene therapy began as more and more scientists sought to conduct clinical trial (testing in humans) research in this area. In that same year, gene therapy was tested on patients with melanoma (skin cancer). The goal was to help them produce antibodies (disease fighting substances in the immune system) to battle the cancer.

These experiments have spawned an ever growing number of attempts at gene therapies designed to perform a variety of functions in the body. For example, a gene therapy for cystic fibrosis aims to supply a gene that alters cells, enabling them to produce a specific protein to battle the disease. Another approach was used for brain cancer patients, in which the inserted gene was designed to make the cancer cells more likely to respond to drug treatment. Gene therapy for patients who have artery blockage, which can lead to strokes, induces the growth of new blood vessels near clogged arteries, thus ensuring normal blood circulation.

Currently, there are a host of new gene therapy agents in clinical trials. In the United States, both nucleic acid-based (*in vivo*) treatments and cell-based (*ex vivo*) treatments are being investigated. Nucleic acid-based gene therapy uses vectors (like viruses) to deliver modified genes to target cells. Cell-based gene therapy techniques remove cells from the patient in order to genetically alter them then reintroduce them to the patient's body. Presently, gene therapies for the following diseases are being developed: cystic fibrosis (using adenoviral vector), HIV infection (cell-based), malignant melanoma (cell-based), **Duchenne muscular dystrophy** (cell-based), hemophilia B (cell-based), kidney cancer (cell-based), **Gaucher disease** (retroviral vector),

breast cancer (retroviral vector), and lung cancer (retroviral vector). When a cell or individual is treated using gene therapy and successful incorporation of engineered genes has occurred, the cell or individual is said to be *transgenic*.

The medical establishment's contribution to transgenic research has been supported by increased government funding. In 1991, the U.S. government provided $58 million for gene therapy research, with increases in funding of $15–40 million dollars a year over the following four years. With fierce competition over the promise of societal benefit in addition to huge profits, large pharmaceutical corporations have moved to the forefront of transgenic research. In an effort to be first in developing new therapies, and armed with billions of dollars of research funds, such corporations are making impressive strides toward making gene therapy a viable reality in the treatment of once elusive diseases.

Diseases targeted for treatment by gene therapy

The potential scope of gene therapy is enormous. More than 4,200 diseases have been identified as resulting directly from abnormal genes, and countless others that may be partially influenced by a person's genetic makeup. Initial research has concentrated on developing gene therapies for diseases whose genetic origins have been established and for other diseases that can be cured or ameliorated by substances genes produce.

The following are examples of potential gene therapies. People suffering from cystic fibrosis lack a gene needed to produce a salt-regulating protein. This protein regulates the flow of chloride into epithelial cells, (the cells that line the inner and outer skin layers) which cover the air passages of the nose and lungs. Without this regulation, patients with cystic fibrosis build up a thick mucus that makes them prone to lung infections. A gene therapy technique to correct this abnormality might employ an adenovirus to transfer a normal copy of what scientists call the cystic fibrosis transmembrane conductance regulator, or CTRF, gene. The gene is introduced into the patient by spraying it into the nose or lungs.

Familial hypercholesterolemia (FH) is also an inherited disease, resulting in the inability to process cholesterol properly, which leads to high levels of artery-clogging fat in the blood stream. Patients with FH often suffer heart attacks and strokes because of blocked arteries. A gene therapy approach used to battle FH is much more intricate than most gene therapies because it involves partial surgical removal of patients' livers (*ex vivo* transgene therapy). Corrected copies of a gene that serve to reduce cholesterol build-up are inserted into the liver sections, which are then transplanted back into the patients.

Gene therapy has also been tested on patients with AIDS. AIDS is caused by the human immunodeficiency virus (HIV), which weakens the body's immune system to the point that sufferers are unable to fight off diseases like pneumonias and cancer. In one approach, genes that produce specific HIV proteins have been altered to stimulate immune system functioning without causing the negative effects that a complete HIV molecule has on the immune system. These genes are then injected in the patient's blood stream. Another approach to treating AIDS is to insert, via white blood cells, genes that have been genetically engineered to produce a receptor that would attract HIV and reduce its chances of replicating.

Several cancers also have the potential to be treated with gene therapy. A therapy tested for melanoma, or skin cancer, involves introducing a gene with an anticancer protein called tumor necrosis factor (TNF) into test tube samples of the patient's own cancer cells, which are then reintroduced into the patient. In brain cancer, the approach is to insert a specific gene that increases the cancer cells' susceptibility to a common drug used in fighting the disease.

Gaucher disease is an inherited disease caused by a mutant gene that inhibits the production of an enzyme called glucocerebrosidase. Patients with Gaucher disease have enlarged livers and spleens and eventually their bones deteriorate. Clinical gene therapy trials focus on inserting the gene for producing this enzyme.

Gene therapy is also being considered as an approach to solving a problem associated with a surgical procedure known as balloon angioplasty. In this procedure, a stent (in this case, a type of tubular scaffolding) is used to open the clogged artery. However, in response to the trauma of the stent insertion, the body initiates a natural healing process that produces too many cells in the artery and results in restenosis, or reclosing of the artery. The gene therapy approach to preventing this unwanted side effect is to cover the outside of the stents with a soluble gel. This gel contains vectors for genes that reduce this overactive healing response.

The Human Genome Project

Although great strides have been made in gene therapy in a relatively short time, its potential usefulness has been limited by lack of scientific data concerning the multitude of functions that genes control in the human body. For instance, it is now known that the vast majority of genetic material does not store information for the creation of proteins, but rather is involved in the control and regulation of gene expression, and is therefore much

more difficult to interpret. Even so, each individual cell in the body carries thousands of genes coding for proteins, with some estimates as high as 150,000 genes. For gene therapy to advance to its full potential, scientists must discover the biological role of each of these individual genes and where the base pairs that make them up are located on DNA.

To address this issue, the National Institutes of Health initiated the **Human Genome Project** in 1990. Led by James D. Watson (one of the co-discoverers of the chemical makeup of DNA), the project's 15-year goal is to map the entire human genome (a combination of the words gene and chromosomes). A genome map would clearly identify the location of all genes as well as the more than three billion base pairs that make them up. With a precise knowledge of gene locations and functions, scientists may one day be able to conquer or control diseases that have plagued humanity for centuries.

Scientists participating in the Human Genome Project have identified an average of one new gene a day, but many expect this rate of discovery to increase. By the year 2005, their goal is to determine the exact location of all the genes on human DNA and the exact sequence of the base pairs that make them up. Some of the genes identified through this project include a gene that predisposes people to obesity, one associated with programmed cell death (apoptosis), a gene that guides HIV viral reproduction, and the genes of inherited disorders like Huntington's disease, Lou Gehrig's disease, and some colon and breast cancers. In February of 2001, scientists published a rough draft of the complete human genome. With fewer than the anticipated number of genes found, between 30,000–40,000, the consequences of this announcement are enormous. Scientists caution however, that the initial publication is only a draft of the human genome and much more work is still ahead for the completion of the project. As the human genome is completed, there will be more information available for gene therapy research and implementation.

The future of gene therapy

Gene therapy seems elegantly simple in its concept: supply the human body with a gene that can correct a biological malfunction that causes a disease. However, there are many obstacles and some distinct questions concerning the viability of gene therapy. For example, viral vectors must be carefully controlled lest they infect the patient with a viral disease. Some vectors, like retroviruses, can also enter cells functioning properly and interfere with the natural biological processes, possibly leading to other diseases. Other viral vectors, like the adenoviruses, are often recognized and destroyed by the immune system so their therapeutic effects are short-lived. Maintaining gene expression so it performs its role properly after vector delivery is difficult. As a result, some therapies need to be repeated often to provide long-lasting benefits.

One of the most pressing issues, however, is gene regulation. Genes work in concert to regulate their functioning. In other words, several genes may play a part in turning other genes on and off. For example, certain genes work together to stimulate cell division and growth, but if these are not regulated, the inserted genes could cause tumor formation and cancer. Another difficulty is learning how to make the gene go into action only when needed. For the best and safest therapeutic effort, a specific gene should turn on, for example, when certain levels of a protein or enzyme are low and must be replaced. But the gene should also remain dormant when not needed to ensure it doesn't oversupply a substance and disturb the body's delicate chemical makeup.

One approach to gene regulation is to attach other genes that detect certain biological activities and then react as a type of automatic off-and-on switch that regulates the activity of the other genes according to biological cues. Although still in the rudimentary stages, researchers are making headway in inhibiting some gene functioning by using a synthetic DNA to block gene transcriptions (the copying of genetic information). This approach may have implications for gene therapy.

The ethics of gene therapy

While gene therapy holds promise as a revolutionary approach to treating disease, ethical concerns over its use and ramifications have been expressed by scientists and lay people alike. For example, since much needs to be learned about how these genes actually work and their long-term effect, is it ethical to test these therapies on humans, where they could have a disastrous result? As with most clinical trials concerning new therapies, including many drugs, the patients participating in these studies have usually not responded to more established therapies and are often so ill the novel therapy is their only hope for long-term survival.

Another questionable outgrowth of gene therapy is that scientists could possibly manipulate genes to genetically control traits in human offspring that are not health related. For example, perhaps a gene could be inserted to ensure that a child would not be bald, a seemingly harmless goal. However, what if genetic manipulation was used to alter skin color, prevent homosexuality, or ensure good looks? If a gene is found that can enhance intelligence of children who are not yet born, will everyone in society, the rich and the poor, have access to the technology or will it be so expensive only the elite can afford it?

The Human Genome Project, which plays such an integral role for the future of gene therapy, also has social repercussions. If individual genetic codes can be determined, will such information be used against people? For example, will someone more susceptible to a disease have to pay higher insurance premiums or be denied health insurance altogether? Will employers discriminate between two potential employees, one with a "healthy" genome and the other with genetic abnormalities?

Some of these concerns can be traced back to the eugenics movement popular in the first half of the twentieth century. This genetic "philosophy" was a societal movement that encouraged people with "positive" traits to reproduce while those with less desirable traits were sanctioned from having children. Eugenics was used to pass strict immigration laws in the United States, barring less suitable people from entering the country lest they reduce the quality of the country's collective **gene pool**. Probably the most notorious example of eugenics in action was the rise of Nazism in Germany, which resulted in the Eugenic Sterilization Law of 1933. The law required sterilization for those suffering from certain disabilities and even for some who were simply deemed "ugly." To ensure that this novel science is not abused, many governments have established organizations specifically for overseeing the development of gene therapy. In the United States, the Food and Drug Administration and the National Institutes of Health requires scientists to take a precise series of steps and meet stringent requirements before approving clinical trials.

In fact, gene therapy has been immersed in more controversy and surrounded by more scrutiny in both the health and ethical arena than most other technologies (except, perhaps, for cloning) that promise to substantially change society. Despite the health and ethical questions surrounding gene therapy, the field will continue to grow and is likely to change medicine faster than any previous medical advancement.

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WEBSITES

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Katherine Hunt, MS

Genetic counseling

Definition

Genetic counseling is a communication process by which personal genetic risk information is translated into practical information for families. Genetic counselors are health care professionals with specialized training and experience in the areas of medical genetics and counseling. Genetic counselors are able to assist families by:

- Helping families understand information about birth defects or **genetic disorders**. This includes explaining patterns of **inheritance**, recurrence risks, natural history of diseases, and **genetic testing** options.
- Providing nondirective supportive counseling regarding emotional issues related to a diagnosis or testing options.
- Helping individuals or families make decisions that they are comfortable with based on their personal ethical and religious standards.
- Connecting families with appropriate resources, such as support groups or specific types of medical clinics, locally and nationally.

Types of genetic counseling

Genetic counselors work with people concerned about the risk of an inherited disease. These patients represent several different patient populations. Prenatal genetic counseling is provided to couples that have an increased risk for birth defects or inherited conditions

KEY TERMS

Canavan disease—A serious genetic disease more common in the Eastern European Jewish population that causes mental retardation and early death. Canavan disease is caused by the lack of an enzyme called aspartoacylase.

Cystic fibrosis—A respiratory disease characterized by chronic lung disease, pancreatic insufficiency and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encode a transmembrane receptor.

Dysmorphic feature—A subtle change in appearance such as low set ears or a flattened nasal bridge that suggests a genetic syndrome may be present.

Fragile X syndrome—A condition caused by an abormality of a region on the X chromosome which may be expressed in males or females, and may increase in severity when inherited from the mother.

Human Genome Project—An international collaborative project among scientists to map the genetic sequence of all the chromosomes. This project is funded by the National Institute of Health in the United States.

Informed consent—Provision of complete information to a competent individual regarding a treatment or test. Part of informed consent is to ensure a patient's understanding of the pros and cons of a procedure and to get their voluntary authorization to perform the procedure.

Sickle cell anemia—A chronic, inherited blood disorder characterized by sickle-shaped red blood cells. It occurs primarily in people of African descent, and produces symptoms including episodic pain in the joints, fever, leg ulcers, and jaundice.

Tay-Sachs disease—An inherited biochemical disease caused by lack of a specific enzyme in the body. In classical Tay-Sachs disease, previously normal children become blind and mentally handicapped, develop seizures, and decline rapidly. Death often occurs between the ages of three to five years. Tay-Sachs disease is common among individuals of eastern European Jewish background but has been reported in other ethnic groups.

Thalassemia—An inherited group of anemias occurring primarily among people of Mediterranean descent. It is caused by defective formation of part of the hemoglobin molecule.

and are expecting a child or planning a pregnancy. Pediatric genetic counseling is provided to families with children suspected of having a genetic disorder or with children previously diagnosed with a genetic disorder. Adult genetic counseling is provided to adults with clinical features of an inherited disease or a family history of an inherited disease. **Cancer** genetic counseling is provided to those with a strong family history of certain types of cancer.

Prenatal genetic counseling

There are several different reasons a person or couple may seek prenatal genetic counseling. If a woman is age 35 or older and pregnant, there is an increased chance that the fetus may have a change in the number of **chromosomes** present. Changes in chromosome number may lead to mental retardation and birth defects. **Down syndrome** is the most common change in chromosome number that occurs more often in the fetuses of older women. Couples may seek prenatal genetic counseling because of abnormal results of screening tests performed during pregnancy. A blood test called the alpha fetal protein (AFP) test is offered to all pregnant women. This blood test screens for Down syndrome, open spine defects (**spina bifida**) and another type of mental retardation caused by a change in chromosome number called **Trisomy 18**. When this test is abnormal, further tests are offered to get more information about the chance of these conditions in the fetus. Another reason that people seek prenatal genetic counseling is a family history of birth defects or inherited diseases. In some cases, blood tests on the parents may be available to indicate if their children would be at risk of being affected. Genetic counselors assess risk in each case, help patients understand their risks and explore how patients feel about or cope with these risks.

Prenatal tests that are offered during genetic counseling include level II ultrasounds, maternal serum AFP screening, chorionic villus sampling (CVS), and **amniocentesis**. Level II ultrasound is a detailed ultrasound surveying fetal anatomy for birth defects. Ultrasound is limited to detection of structural changes in anatomy and cannot detect changes in chromosome number. The maternal serum AFP screening is used to indicate if a pregnant woman has a higher or lower chance of certain birth defects. This test can only change the chances for a

birth defect. The screening cannot diagnose a birth defect. CVS is a way of learning how many chromosomes is present in a fetus. A small piece of placental tissue is obtained for these studies during the tenth to twelfth weeks of pregnancy. Amniocentesis is also a way of learning how many chromosomes are present in a fetus. Amniotic fluid is obtained for these studies, usually between 16 and 18 weeks of pregnancy. There is a small risk for miscarriage with both of these tests. Genetic counseling regarding these procedures involves the careful explanation of benefits and limitations of each testing option. The counselor also tries to explore how patients feel about prenatal testing and the impact of such testing on the pregnancy. Genetic counselors are supportive of any decision a patient makes about whether or not to have prenatal tests performed.

Pediatric genetic counseling

Families or pediatricians seek genetic counseling when a child has features of an inherited condition. Any child who is born with more than one birth defect, mental retardation, or dysmorphic features has an increased chance of having a genetic syndrome. A common type of mental retardation in males for which genetic testing is available is **fragile X syndrome**. Genetic testing is also available for many other childhood illnesses such as **hemophilia** and **muscular dystrophy**. Genetic counselors work with medical geneticists to determine if a genetic syndrome is present. This process includes a careful examination of family history, medical history of the child, review of pertinent medical records in the family, a physical examination of the child, and sometimes blood work or other diagnostic tests. If a diagnosis is made, then the medical geneticist and genetic counselor review what is known about the inheritance of the condition, the natural history of the condition, treatment options, further examinations that may be needed for health problems common in the diagnosed syndrome and resources for helping the family. The genetic counselor also helps the family adjust to the diagnosis by emotional support and counseling. Many families are devastated by receiving a diagnosis, learning of the likely outcome for the child, and by the loss of the hoped-for healthy child. There would also be a discussion about recurrence risks in the family and who else in the family may be at risk.

Adult genetic counseling

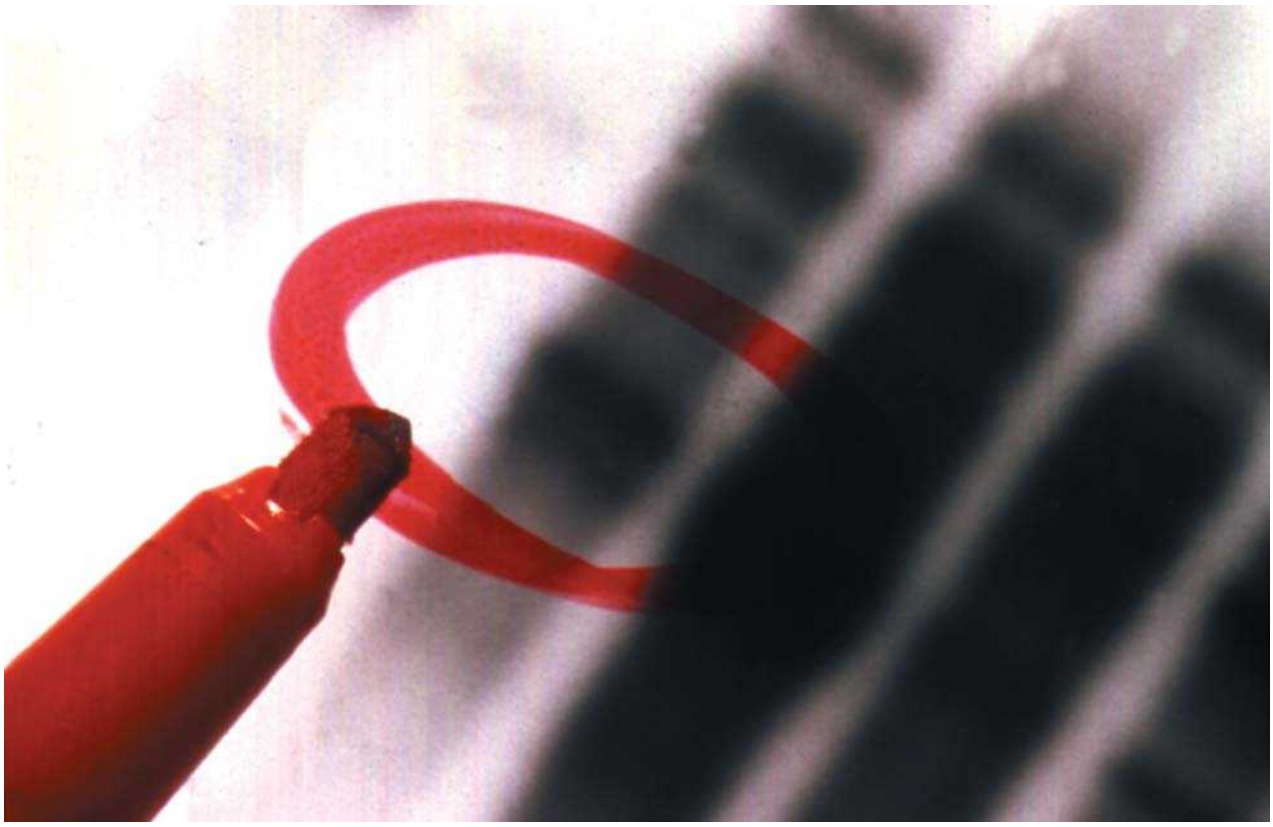
Adults seek genetic counseling when a person in the family decides to be tested for a known genetic condition in the family, when an adult begins exhibiting symptoms of an inherited condition or when there is a new diagnosis of someone with an adult onset disorder in the family. In addition, sometimes the birth of a child with obvious features of a genetic disease leads to diagnosis of a parent who is affected more mildly. Genetic counseling for adults may lead to the consideration of presymptomatic genetic testing. Testing a person to determine if they will be symptomatic for a condition before the symptoms occur is an area of controversy. **Huntington disease** is an example of a genetic disease for which presymptomatic testing is available. Huntington disease is a neurological disease resulting in **dementia**. Onset of the condition is between 30 to 50 years of age. Huntington disease is inherited in an autosomal dominant pattern. If a person has a parent with the disease, their risk of being affected is 50%. Would presymptomatic testing relieve or create anxiety? Would a person benefit from removal of doubt about being affected? Would knowing help a person with life planning? Genetic counselors help patients sort through their feelings about such testing and whether or not the results would be helpful to them.

Cancer genetic counseling

A family history of early onset breast, ovarian, or colon cancer in multiple generations of a family is a common reason a person would seek a genetic counselor that works with cancer patients. While most cancer is not inherited, there are some families in which a dominant **gene** is present and causing the disease. The genetic counselor is able to discuss with a patient the chance that the cancer in the family is related to a dominantly inherited gene. The counselor can also discuss the option of testing for the breast and **ovarian cancer** genes, BRCA1 and BRCA2. In some cases the person seeking testing has already had cancer, and in others they have not. Therefore, presymptomatic testing is also an issue in cancer genetics. Emotional support is important for these patients as they have often lost close relatives from cancer and are fearful of their own risks. For families in which a dominant form of cancer is detected through genetic testing, a plan for increased surveillance for the disease can be made.

The pedigree

In all types of genetic counseling, an important aspect of the genetic counseling session is information gathering about family and medical history. Information gathering is performed by drawing a chart called a pedigree. A pedigree is made of symbols and lines that represent the family history. To accurately assess the risk of inherited diseases, information about three generations of the family, including health status and/or cause of death, is usually needed. If the family history is complicated, information from more distant relatives may be helpful, and medical records may be requested for any family



DNA sequencing is used to detect similarities and differences between gene sequences of family members. *(Custom Medical Stock Photo, Inc.)*

members who have had a genetic disorder. Through an examination of the family history a counselor may be able to discuss the probability of future occurrence of genetic disorders.

Ethnicity

In taking a family history, a genetic counselor asks the patient's ethnicity or ancestral origin. There are some ethnic groups that have a higher chance of being carriers of some genetic diseases. For instance, the chance that an African American is a carrier of a gene for sickle cell disease is 1/10. People of Jewish ancestry are more likely to be carriers of several conditions including **Tay-Sachs disease**, **Canavan disease,** and **cystic fibrosis**. People of Mediterranean ancestry are more likely to be carriers of a type of anemia called **thalassemia**. Genetic counselors discuss inheritance patterns of these diseases, carrier risks, and genetic screening or testing options.

Consanguinity

Another question a genetic counselor asks in taking a family history is if the couple is related to one another by blood. The practice of marrying or having children with relatives is infrequent in the United States, but is more common in some countries. When two people are related by blood, there is an increased chance for their children to be affected with conditions inherited in a recessive pattern. In recessive inheritance, each parent of a child affected with a disease carries a single gene for the disease. The child gets two copies, one from each parent, and is affected. People who have a common ancestor are more likely than unrelated people to be carriers of genes for the same recessively inherited genes. Depending on family history and ethnic background, blood tests can be offered to couples to get more information about the chance for these conditions to occur.

Exposures during pregnancy

During prenatal genetic counseling, the counselor will ask about pregnancy history. If the patient has taken a medication or has had a harmful exposure (like radiation), the genetic counselor can discuss the possibility of harmful affects. Ultrasound is often a useful tool to look for some affects of exposures.

Ethical issues in genetic counseling

Prenatal diagnosis of anomalies or **chromosomal abnormalities** leads to a decision about whether or not a couple wishes to continue a pregnancy. Some couples chose to continue a pregnancy. Prenatal diagnosis gives them additional time to emotionally prepare for the birth of the child and to gather resources. Others choose not to continue a pregnancy in which problems have been diagnosed. These couples have unique emotional needs. Often the child is very much a desired addition to the family and parents are devastated that the child is not healthy. Presymptomatic testing for adult onset disorders and cancer raise difficult issues regarding the need to know and the reality of dealing with abnormal results before symptoms. The National Society of Genetic Counselors has created a Code of Ethics to guide genetic counselors in caring for patients. The Code of Ethics consists of four ethical principles:

- Beneficience is the promotion of personal well being in others. The genetic counselor is an advocate for the patient.
- Nonmaleficience is the idea of doing no harm to a patient.
- Autonomy is recognizing the value of the individual, the person's abilities, and their point of view. Important aspects of autonomy are truthfulness with patients, respecting confidentiality, and practicing informed consent.
- Justice is providing equal care for all, freedom of choice, and providing a high quality of care.

Perhaps the main ethical principle of genetic counseling is the attempt to provide nondirective counseling. This principle again points to a patient centered approach to care by focusing on the thoughts and feelings of the patient. Five percent of the **Human Genome Project** budget is designated to research involving the best way to deal with ethical issues that arise as new genetic tests become available. Genetic counselors can help patients navigate through the unfamiliar territory of genetic testing.

Resources

BOOKS

Baker, Diane. *A Guide to Genetic Counseling*. New York: John Wiley and Sons, Inc., 1998.

Harper, Peter S. *Practical Genetic Counseling.* Oxford: Butterworth Heinmann, 1998.

ORGANIZATIONS

American Society of Human Genetics. 9650 Rockville Pike, Bethesda, MD 20814-3998. (301) 571-1825. <http://www.faseb.org/genetics/ashg/ashgmenu.htm>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. <http://www.nsgc.org/GeneticCounselingYou.asp>.

Sonja Rene Eubanks, MS, CGC

Genetic disorders

Variations within the **DNA** sequence of a particular **gene** affect its function and may cause or predispose an individual a particular disease. Alterations in the genome may increase the frequency of disorder and disease with entire populations.

Although there are many types of genetic disorders, a specific disorder does not have to be inheritable to have a genetic basis. For example, non-heritable disorders can also arise from mutations in somatic cells resulting from exposure to mutagenic factors in the environment. Mutations, whether inherited mutations that appear in every cell of the body, or random mutations affecting a particular cell, can cause groups of cells to grow out of control or inhibit the processes (contact inhibition processes) that normally prevent this from happening.

Some diseases and disorders are traced to the presence of a single form of a gene, to a mutation in a specific normal gene. Other common conditions, including not only some cancers but also some forms of heart disease and diabetes, are polygenic. Variations in a number of genes, in combination with environmental conditions that determine the extent to which these genes are expressed, affect the risk that an individual will develop such conditions. The risk calculations associated with many of the disorders commonly regarded as genetic diseases are often predictable as functions of relatively simple Mendelian inheritance.

There are many types of genetic diseases and disorders result from a few well-established mechanisms. Autosomal dominant disorders, in which one deleterious gene or allele expresses itself over a normal complementary allele is normal is the mechanism underlying Crouzon's disease. In contrast, phenylketonuria, is an autosomal recessive disorder, in which both deleterious alleles must be present. There are also sex-linked diseases and disorders wherein the deleterious gene or genes lie on sex **chromosomes** (X and Y chromosomes). There are X-linked dominant disorders (e.g., hypoplastic amelogenesis imperfecta), X-linked recessive disorders

(Menkes' syndrome), and Y-linked disorders, in which the only mechanism of transmission is from father to son.

Not all genetic disorders depend on alterations to nuclear DNA. There are disorders, such as mitochondrial myopathy, that can result from alterations to mitochondrial DNA.

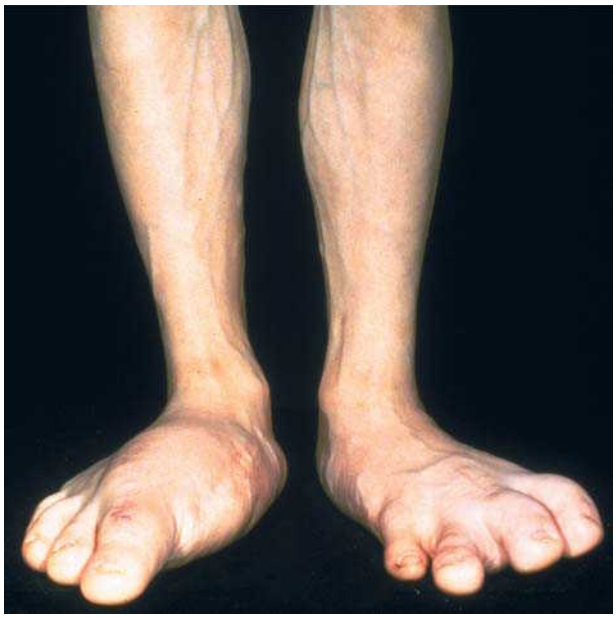
Genetic counseling deals with the problems associated with the diagnosis of a genetic disorder, the probable disease course, and possible treatments and management. **Genetic testing** used to assess the risks of genetic disorders and the risks of recurrence. Options for dealing with the risk of a genetic disorder and its recurrence sometimes involve methods of contraception, adoption, insemination by donor sperm, and prenatal diagnosis.

Bayes' theorem is used in genetic epidemiology in order to obtain the probability of disease in a group of people with some characteristic. In addition, Bayes' theorem is able to calculate unknown conditional probabilities (PVP) from known conditional probabilities (detection rate or sensitivity). For example, biochemical and ultrasound marker-based screening use a derivation of Bayes' theorem to select patients for whom further testing for a particular disease or disorder may be appropriate.

A variation of Bayes' theorem, termed the Bart's test, is very popular in the prenatal screening projects. Bart's test allows an adjustment of the probability of the disease (expressed as 1/total) for an appropriate factor named likelihood ratio, that is the ratio between the detection rate and the false positive rate.

Except for genes appearing on the X or Y chromosomes in males, there are usually two copies of each gene in humans. This redundancy provides a buffer to genetic diseases and disorders. In many cases, only one correctly functioning copy of a gene is necessary. Only when an individual has obtained two copies of a defective recessive gene will the corresponding disease manifest itself. Inheritance of this type is called homozygous recessive.

A heterozygous individual with one allele for such a condition may be completely unaffected. In other cases, the individual may even be at an advantage, which provides a clue as to why the mutation remains in the population. Sickle cell disease, relatively common among people of African descent, is an often-fatal condition in which red blood cells become sickle-shaped when the oxygen content of the blood decreases, as it does during physical exertion. The deformed blood cells block small blood vessels, causing tissue death (necrosis) in affected areas. Although only an individual with two alleles for sickle cell will have the disease, individuals with one sickle cell allele (type pf gene) have sickle cell trait. Trait carriers only experience disease-like symptoms at extreme low-oxygen conditions such as those found at very high altitudes. On the other hand, such an individual actually gains a significant advantage relative to malarial resistance. Malaria is endemic in Africa, and the evolutionary benefit of having a large population of people who are heterozygous for the trait overcomes the disadvantage of a fatal condition affecting homozygotes with two copies of the allele. Therefore this type of genetic disease may persist at a relatively high frequency in a population over a long period of time even if the actual disorder is serious or potentially fatal.



Abnormal formation of body systems and parts, for instance the giantisim of feet, often assists with diagnosis of specific inherited disorders. *(Custom Medical Stock Photos, Inc.)*

With dominant alleles, one copy of a defective gene is enough to produce a disease or disorder. Genetic disorders with dominant inheritance that are lethal at an early age do not remain in the population, because they kill the affected individual before he or she can reproduce. However, nonlethal dominant genetic disorders, such as the hand and foot malformation called camptobrachydactyly, do persist over time. Likewise, a lethal genetic disorder such as Huntington's disease that strikes after the individual has reached reproductive maturity can also be passed along to future generations.

If the gene associated with a disorder is found on the X chromosome, typically males are afflicted more often and/or more severely than females. That is because in females who are heterozygous for such an X-linked trait, there is a normal version of the gene to compensate.

Males have only one X chromosome, so if a X-linked gene is mutated, it usually has a severe effect. X-linked genetic disorders include **hemophilia** and red-green **color blindness**.

Chromosome abnormalities, such as the addition or deletion of a chromosome, may result from errors that occur when gametes (sperm and egg) are formed, during fertilization, or during the early development of the zygote. Most chromosome aberrations are lethal, resulting in spontaneous abortion (miscarriage), or death in infancy. Only a few, including the extra copy of chromosome 21 that results in **Down syndrome**, produces individuals who, although affected by mental and physical abnormalities, can survive into adulthood.

Abdel Hakim Ben Nasr, PhD

Genetic screening *see* **Genetic testing**

Genetic testing

Definition

A genetic test examines the genetic information contained inside a person's cells, called **DNA**, to determine if that person has or will develop a certain disease or could pass a disease to his or her offspring. Genetic tests also determine whether or not couples are at a higher risk than the general population for having a child affected with a genetic disorder.

Purpose

Some families or ethnic groups have a higher incidence of a certain disease than does the population as a whole. For example, individuals from Eastern European, Ashkenazi Jewish descent are at higher risk for carrying genes for rare conditions that occur much less frequently in populations from other parts of the world. Before having a child, a couple from such a family or ethnic group may want to know if their child would be at risk of having that disease. Genetic testing for this type of purpose is called genetic screening.

During pregnancy, the baby's cells can be studied for certain **genetic disorders** or chromosomal problems such as **Down syndrome**. Chromosome testing is most commonly offered when the mother is 35 years or older at the time of delivery. When there is a family medical history of a genetic disease or there are individuals in a family affected with developmental and physical delays, genetic testing may also be offered during pregnancy. Genetic testing during pregnancy is called prenatal diagnosis.

Prior to becoming pregnant, couples who are having difficulty conceiving a child or who have suffered multiple miscarriages may be tested to see if a genetic cause can be identified.

A genetic disease may be diagnosed at birth by doing a physical evaluation of the baby and observing characteristics of the disorder. Genetic testing can help to confirm the diagnosis made by the physical evaluation. In addition, genetic testing is used routinely on all newborns to screen for certain genetic diseases which can affect a newborn baby's health shortly after birth.

There are several genetic diseases and conditions in which the symptoms do not occur until adulthood. One such example is Huntington's disease. This is a serious disorder affecting the way in which individuals walk, talk, and function on a daily basis. Genetic testing may be able to determine if someone at risk for the disease will in fact develop the disease.

Some genetic defects may make a person more susceptible to certain types of **cancer**. Testing for these defects can help predict a person's risk. Other types of genetic tests help diagnose and predict and monitor the course of certain kinds of cancer, particularly leukemia and lymphoma.

Precautions

Because genetic testing is not always accurate and because there are many concerns surrounding insurance and employment discrimination for the individual receiving a genetic test, **genetic counseling** should always be performed prior to genetic testing. A genetic counselor is an individual with a master's degree in genetic counseling. A medical geneticist is a physician specializing and board certified in genetics.

A genetic counselor reviews the person's family history and medical records and the reason for the test. The counselor explains the likelihood that the test will detect all possible causes of the disease in question (known as the sensitivity of the test), and the likelihood that the disease will develop if the test is positive (known as the positive predictive value of the test).

Learning about the disease in question, the benefits and risks of both a positive and a negative result, and what treatment choices are available if the result is positive, will help prepare the person undergoing testing. During the genetic counseling session, the individual interested in genetic testing will be asked to consider how the test results will affect his or her life, family, and future decisions.

After this discussion, the person should have the opportunity to indicate in writing that he or she gave informed consent to have the test performed, verifying that the counselor provided complete and understandable information.

Background

Genes and chromosomes

Deoxyribonucleic acid (DNA) is a long molecule made up of two strands of genetic material coiled around each other in a unique double helix structure. This structure was discovered in 1953 by Francis Crick and James Watson.

DNA is found in the nucleus, or center, of most cells (some cells, such as a red blood cell, don't have a nucleus). Each person's DNA is a unique blueprint, giving instructions for a person's physical traits, such as eye color, hair texture, height, and susceptibility to disease. DNA is organized into structures called **chromosomes**.

The instructions are contained in DNA's long strands as a code spelled out by pairs of bases, which are four chemicals that make up DNA. The bases occur as pairs because a base on one strand lines up with and is bound to a corresponding base on the other strand. The order of these bases form DNA's code. The order of the bases on a DNA strand is important to ensuring that a person is not affected with any genetic disorders. When the bases are out of order or missing, cells often may not produce important proteins; this can lead to a genetic disorder. While genes are found in every cell of the body, not every **gene** is functioning all of the time. Some genes are turned on during critical points in development and then remain silent for the rest of the individual's life. Other genes always remain active so that cells can produce important proteins such as those that help digest food properly or fight off the common cold.

The specific order of the base pairs on a strand of DNA is important in order for the correct protein to be produced. A grouping of three base pairs on the DNA strand is called a codon. Each codon, or three base pairs, comes together to spell a word. A string of many codons together can be thought of as a series of words all coming together to make a sentence. This sentence is what instructs cells to make a protein that helps bodies function properly.

DNA strands containing a hundred to several thousand copies of genes are found on structures called chromosomes. Each cell typically has 46 chromosomes arranged into 23 pairs. Each parent contributes one chromosome to each pair. The first 22 pairs are called autosomal chromosomes, or non-sex chromosomes and are assigned a number from 1–22. The last pair are the sex chromosomes and include the X and the Y chromosomes. If a child receives an X chromosome from each parent, the child is female. If a child receives an X from the mother, and a Y from the father, the child is male.

Just as each parent contributes one chromosome to each pair, so each parent contributes one gene from each chromosome. The pair of genes produces a specific trait in the child. In autosomal dominant conditions, it takes only one copy of a gene to influence a specific trait. The stronger gene is called dominant; the weaker gene is called recessive. Two copies of a recessive gene are needed to control a trait, while only one copy of a dominant gene is needed. Our sex chromosomes, the X and the Y, also contain important genes. Some genetic diseases are caused by missing or altered genes on one of the sex chromosomes. Males are most often affected by sex chromosome diseases when they inherit an X chromosome with missing or mutated genes from their mother.

Types of genetic mutations

Genetic disease results from a change, or mutation, in a chromosome or in one or several base pairs on a gene. Some of us inherit these mutations from our parents, called hereditary or germline mutations, while other mutations can occur spontaneously, or for the first time in an affected child. For many of the adult on-set diseases, genetic mutations can occur over the lifetime of the individual. This is called acquired or somatic mutations, and these occur while the cells are making copies of themselves or dividing in two. There may be some environmental effects, such as radiation or other chemicals, that can contribute to these types of mutations as well.

There are a variety of different types of mutations that can occur in the genetic code to cause a disease. And for each genetic disease, there may be more than one type of mutation to cause the disease. For some genetic diseases, the same mutation occurs in every individual affected with the disease. For example, the most common form of dwarfism, called **achondroplasia**, occurs because of a single base pair substitution. This same mutation occurs in all individuals affected with the disease. Other genetic diseases are caused by different types of genetic mutations that may occur anywhere along the length of a gene. For example, **cystic fibrosis**, the most common genetic disease in the caucasian population, is caused by hundreds of different mutations along the gene. Individual families may carry the same mutation as each other, but not as the rest of the population affected with the same genetic disease.

Some genetic diseases occur as a result of a larger mutation that can occur when the chromosome itself is

either rearranged or altered or when a baby is born with more than the expected number of chromosomes. There are only a few types of chromosome rearrangements that are possibly hereditary, or passed on from the mother or the father. The majority of chromosome alterations occur sporadically or for the first time with a new baby.

The type of mutation that causes a genetic disease will determine the type of genetic test to be performed. In some situations, more than one type of genetic test will be performed to arrive at a diagnosis. The cost of genetic tests vary: chromosome studies can cost hundreds of dollars and certain gene studies can cost thousands. Insurance coverage also varies with the company and the policy. It may take several days or several weeks to complete a test. Research testing where the exact location of a gene has not yet been identified can take several months or years for results.

Types of genetic testing

Direct DNA mutation analysis

Direct DNA sequencing examines the direct base pair sequence of a gene for specific gene mutations. Some genes contain more than 100,000 bases, and a mutation of any one base can make the gene nonfunctional and cause disease. The more mutations possible, the less likely it is for a test to detect all of them. This test is usually done on white blood cells from a person's blood, but can also be performed on other tissues. There are different ways in which to perform direct DNA mutation analysis. When the specific genetic mutation is known, it is possible to perform a complete analysis of the genetic code, also called direct sequencing. There are several different lab techniques used to test for a direct mutation. One common approach begins by using chemicals to separate DNA from the rest of the cell. Next, the two strands of DNA are separated by heating. Special enzymes (called restriction enzymes) are added to the single strands of DNA; they act like scissors and cut the strands in specific places. The DNA fragments are then sorted by size through a process called electrophoresis. A special piece of DNA, called a probe, is added to the fragments. The probe is designed to bind to specific mutated portions of the gene. When bound to the probe, the mutated portions appear on x-ray film with a distinct banding pattern.

Indirect DNA Testing

Family linkage studies are done to study a disease when the exact type and location of the genetic alteration is not known, but the general location on the chromosome has been identified. These studies are possible when a chromosome marker has been found associated with a disease. Chromosomes contain certain regions that vary in appearance between individuals. These regions are called polymorphisms and do not cause a genetic disease to occur. If a polymorphism is always present in family members with the same genetic disease, and absent in family members without the disease, it is likely that the gene responsible for the disease is near that polymorphism. The **gene mutation** can be indirectly detected in family members by looking for the polymorphism.

To look for the polymorphism, DNA is isolated from cells in the same way it is for direct DNA mutation analysis. A probe is added that will detect the large polymorphism on the chromosome. When bound to the probe, this region will appear on x-ray film with a distinct banding pattern. The pattern of banding of a person being tested for the disease is compared to the pattern from a family member affected by the disease.

Linkage studies have disadvantages not found in direct DNA mutation analysis. These studies require multiple family members to participate in the testing. If key family members choose not to participate, the incomplete family history may make testing other members useless. The indirect method of detecting a mutated gene also causes more opportunity for error.

Chromosome analysis

Various genetic syndromes are caused by structural chromosome abnormalities. To analyze a person's chromosomes, his or her cells are allowed to grow and multiply in the laboratory until they reach a certain stage of growth. The length of growing time varies with the type of cells. Cells from blood and bone marrow take 1–2 days; fetal cells from amniotic fluid take 7–10 days.

When the cells are ready, they are placed on a microscope slide using a technique to make them burst open, spreading their chromosomes. The slides are stained: the stain creates a banding pattern unique to each chromosome. Under a microscope, the chromosomes are counted, identified, and analyzed based on their size, shape, and stained appearance.

A **karyotype** is the final step in the chromosome analysis. After the chromosomes are counted, a photograph is taken of the chromosomes from one or more cells as seen through the microscope. Then the chromosomes are cut out and arranged side-by-side with their partner in ascending numerical order, from largest to smallest. The karyotype is done either manually or using a computer attached to the microscope. Chromosome analysis is also called cytogenetics.

KEY TERMS

Autosomal disease—A disease caused by a gene located on an autosomal chromosome.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Dominant gene—A gene, whose presence as a single copy, controls the expression of a trait.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Positive predictive value (PPV)—The probability that a person with a positive test result has, or will get, the disease.

Recessive gene—A type of gene that is not expressed as a trait unless inherited by both parents.

Sensitivity—The proportion of people with a disease who are correctly diagnosed (test positive based on diagnostic criteria). The higher the sensitivity of a test or diagnostic criteria, the lower the rate of 'false negatives'—people who have a disease but are not identified through the test.

Sex-linked disorder—A disorder caused by a gene located on a sex chromosome, usually the X chromosome.

Applications for genetic testing

Newborn screening

Genetic testing is used most often for newborn screening. Every year, millions of newborn babies have their blood samples tested for potentially serious genetic diseases.

Carrier testing

An individual who has a gene associated with a disease but never exhibits any symptoms of the disease is called a carrier. A carrier is a person who is not affected by the mutated gene he or she possesses, but can pass the gene to an offspring. Genetic tests have been developed that tell prospective parents whether or not they are carriers of certain diseases. If one or both parents are a carrier, the risk of passing the disease to a child can be predicted.

To predict the risk, it is necessary to know if the gene in question is autosomal or sex-linked. If the gene is carried on any one of chromosomes 1–22, the resulting disease is called an autosomal disease. If the gene is carried on the X or Y chromosome, it is called a sex-linked disease.

Sex-linked diseases, such as the bleeding condition **hemophilia**, are usually carried on the X chromosome. A woman who carries a disease-associated gene on one of her X chromosomes has a 50% chance of passing that gene to her son. A son who inherits that gene will develop the disease because he does not have another normal copy of the gene on a second X chromosome to compensate for the abnormal copy. A daughter who inherits the disease-associated gene from her mother will be at risk for having a son affected with the disease.

The risk of passing an autosomal disease to a child depends on whether the gene is dominant or recessive. A prospective parent carrying a dominant gene has a 50% chance of passing the gene to a child. A child needs to receive only one copy of the mutated gene to be affected by the disease.

If the gene is recessive, a child needs to receive two copies of the mutated gene, one from each parent, to be affected by the disease. When both parents are carriers,

their child has a 25% chance of inheriting two copies of the mutated gene and being affected by the disease; a 50% chance of inheriting one copy of the mutated gene, and being a carrier of the disease but not affected; and a 25% chance of inheriting two normal genes. When only one parent is a carrier, a child has a 50% chance of inheriting one mutated gene and being an unaffected carrier of the disease, and a 50% chance of inheriting two normal genes.

Cystic fibrosis is a disease that affects the lungs and pancreas and is discovered in early childhood. It is the most common autosomal recessive genetic disease found in the caucasian population: one in 25 people of Northern European ancestry are carriers of a mutated cystic fibrosis gene. The gene, located on chromosome 7, was identified in 1989.

The gene mutation for cystic fibrosis is detected by a direct DNA test. Over 600 mutations of the cystic fibrosis gene have been found; each of these mutations cause the same disease. Tests are available for the most common mutations. Tests that check for the 86 of the most common mutations in the Caucasian population will detect 90% of carriers for cystic fibrosis. (The percentage of mutations detected varies according to the individual's ethnic background). If a person tests negative, it is likely, but not guaranteed that he or she does not have the gene. Both parents must be carriers of the gene to have a child with cystic fibrosis.

Tay-Sachs disease, also autosomal recessive, affects children primarily of Ashkenazi Jewish descent. Children with this disease die between the ages of two and five. This disease was previously detected by looking for a missing enzyme. The mutated gene has now been identified and can be detected using direct DNA mutation analysis.

Presymptomatic testing

Not all genetic diseases show their effect immediately at birth or early in childhood. Although the gene mutation is present at birth, some diseases do not appear until adulthood. If a specific mutated gene responsible for a late-onset disease has been identified, a person from an affected family can be tested before symptoms appear.

Huntington disease is one example of a late-onset autosomal dominant disease. Its symptoms of mental confusion and abnormal body movements do not appear until middle to late adulthood. The chromosome location of the gene responsible for Huntington's chorea was located in 1983 after studying the DNA from a large Venezuelan family affected by the disease. Ten years later, the gene was identified. A test is now available to detect the presence of the expanded base pair sequence responsible for causing the disease. The presence of this expanded sequence means the person will develop the disease.

Another late onset disease, Alzheimer's, does not have as well a understood genetic cause as Huntington's disease. The specific genetic cause of **Alzheimer disease** is not as clear. Although many cases appear to be inherited in an autosomal dominant pattern, many cases exist as single incidents in a family. Like Huntington's, symptoms of mental deterioration first appear in adulthood. Genetic research has found an association between this disease and genes on four different chromosomes. The validity of looking for these genes in a person without symptoms or without family history of the disease is still being studied.

CANCER SUSCEPTIBILITY TESTING Cancer can result from an inherited (germline) mutated gene or a gene that mutated sometime during a person's lifetime (acquired mutation). Some genes, called tumor suppressor genes, produce proteins that protect the body from cancer. If one of these genes develops a mutation, it is unable to produce the protective protein. If the second copy of the gene is normal, its action may be sufficient to continue production, but if that gene later also develops a mutation, the person is vulnerable to cancer. Other genes, called oncogenes, are involved in the normal growth of cells. A mutation in an **oncogene** can cause too much growth, which is the beginning of cancer.

Direct DNA tests are currently available to look for gene mutations identified and linked to several kinds of cancer. People with a family history of these cancers are those most likely to be tested. If one of these mutated genes is found, the person is more susceptible to developing the cancer. The likelihood that the person will develop the cancer, even with the mutated gene, is not always known because other genetic and environmental factors are also involved in the development of cancer.

Cancer susceptibility tests are most useful when a positive test result can be followed with clear treatment options. In families with familial polyposis of the colon, testing a child for a mutated APC gene can reveal whether or not the child needs frequent monitoring for the disease. In families with potentially fatal familial medullary thyroid cancer or **multiple endocrine neoplasia** type 2, finding a mutated RET gene in a child provides the opportunity for that child to have preventive removal of the thyroid gland. In the same way, MSH1 and MSH2 mutations can reveal which members in an affected family are vulnerable to familiar colorectal cancer and would benefit from aggressive monitoring.

In 1994, a mutation linked to early-onset familial breast and **ovarian cancer** was identified. BRCA1 is

Scientist showing results of gel electrophoresis, a technique used to separate DNA molecules based on their size. *(Photo Researchers, Inc.)*

located on chromosome 17. Women with a mutated form of this gene have an increased risk of developing breast and ovarian cancer. A second related gene, BRCA2, was later discovered. Located on chromosome 13, it also carries increased risk of breast and ovarian cancer. Although both genes are rare in the general population, they are slightly more common in women of Ashkenazi Jewish descent.

When a woman is found to have a mutation in one of these genes, the likelihood that she will get breast or ovarian cancer increases, but not to 100%. Other genetic and environmental factors influence the outcome.

Testing for these genes is most valuable in families where a mutation has already been found. BRCA1 and BRCA2 are large genes; BRCA1 includes 100,000 bases. More than 120 mutations to this gene have been discovered, but a mutation could occur in any one of the bases. Studies show tests for these genes may miss 30% of existing mutations. The rate of missed mutations, the unknown disease likelihood in spite of a positive result, and the lack of a clear preventive response to a positive result make the value of this test for the general population uncertain.

Prenatal and postnatal chromosome analysis

Chromosome analysis is performed on fetal cells primarily when the mother is age 35 or older at the time of delivery, has experienced multiple miscarriages, or reports a family history of a genetic abnormality. Prenatal testing is done on the fetal cells from a chorionic villus sampling (from the baby's developing placenta) at 10–12 weeks or from the amniotic fluid (the fluid surrounding the baby) at 16–18 weeks of pregnancy. Cells from amniotic fluid grow for seven to 10 days before they are ready to be analyzed. Chorionic villi cells have the potential to grow faster and can be analyzed sooner.

Chromosome analysis using blood cells is done on a child who is born with or later develops signs of mental retardation or physical malformation. In the older child, chromosome analysis may be done to investigate developmental delays.

Extra or missing chromosomes cause mental and physical abnormalities. A child born with an extra chromosome 21 (trisomy 21) has Down syndrome. An extra chromosome 13 or 18 also produce well known syndromes. A missing X chromosome causes **Turner syndrome** and an extra X in a male causes **Klinefelter**

syndrome. Other abnormalities are caused by extra or missing pieces of chromosomes. **Fragile X syndrome** is a sex-linked disease that causes mental retardation in males.

Chromosome material may also be rearranged, such as the end of chromosome 1 moving to the end of chromosome 3. This is called a chromosomal translocation. If no material is added or deleted in the exchange, the person may not be affected. Such an exchange, however, can cause infertility or abnormalities if passed to children.

Evaluation of a man and woman's infertility or repeated miscarriages will include blood studies of both to check for a chromosome translocation. Many chromosome abnormalities are incompatible with life; babies with these abnormalities often miscarrry during the first trimester. Cells from a baby that died before birth can be studied to look for chromosome abnormalities that may have caused the death.

Cancer diagnosis and prognosis

Certain cancers, particularly leukemia and lymphoma, are associated with changes in chromosomes: extra or missing complete chromosomes, extra or missing portions of chromosomes, or exchanges of material (translocations) between chromosomes. Studies show that the locations of the chromosome breaks are at locations of tumor suppressor genes or oncogenes.

Chromosome analysis on cells from blood, bone marrow, or solid tumor helps diagnose certain kinds of leukemia and lymphoma and often helps predict how well the person will respond to treatment. After treatment has begun, periodic monitoring of these chromosome changes in the blood and bone marrow gives the physician information as to the effectiveness of the treatment.

A well-known chromosome rearrangement is found in chronic myelogenous leukemia. This leukemia is associated with an exchange of material between chromosomes 9 and 22. The resulting smaller chromosome 22 is called the Philadelphia chromosome.

Preparation

Most tests for genetic diseases of children and adults are done on blood. To collect the 5–10 mL of blood needed, a healthcare worker draws blood from a vein in the inner elbow region. Collection of the sample takes only a few minutes.

Prenatal testing is done either on amniotic fluid or a chorionic villus sampling. To collect amniotic fluid, a physician performs a procedure called **amniocentesis**. An ultrasound is done to find the baby's position and an area filled with amniotic fluid. The physician inserts a needle through the woman's skin and the wall of her uterus and withdraws 5–10 mL of amniotic fluid. Placental tissue for a chorionic villus sampling is taken through the cervix. Each procedure takes approximately 30 minutes.

Bone marrow is used for chromosome analysis in a person with leukemia or lymphoma. The person is given local anesthesia. Then the physician inserts a needle through the skin and into the bone (usually the sternum or hip bone). One-half to 2 mL of bone marrow is withdrawn. This procedure takes approximately 30 minutes.

Aftercare

After blood collection the person can feel discomfort or bruising at the puncture site or may become dizzy or faint. Pressure to the puncture site until the bleeding stops reduces bruising. Warm packs to the puncture site relieve discomfort.

The chorionic villus sampling, amniocentesis, and bone marrow procedures are all done under a physician's supervision. The person is asked to rest after the procedure and is watched for weakness and signs of bleeding.

Risks

Collection of amniotic fluid and chorionic villus sampling, have the risk of miscarriage, infection, and bleeding; the risks are higher for the chorionic villus sampling. Because of the potential risks for miscarriage, 0.5% following the amniocentesis and 1% following the chorionic villus sampling procedure, both of these prenatal tests are offered to couples, but not required. A woman should tell her physician immediately if she has cramping, bleeding, fluid loss, an increased temperature, or a change in the baby's movement following either of these procedures.

After bone marrow collection, the puncture site may become tender and the person's temperature may rise. These are signs of a possible infection.

Genetic testing involves other nonphysical risks. Many people fear the possible loss of privacy about personal health information. Results of genetic tests may be reported to insurance companies and affect a person's insurability. Some people pay out-of-pocket for genetic tests to avoid this possibility. Laws have been proposed to deal with this problem. Other family members may be affected by the results of a person's genetic test. Privacy of the person tested and the family members affected is a consideration when deciding to have a test and to share the results.

A positive result carries a psychological burden, especially if the test indicates the person will develop a

disease, such as Huntington's chorea. The news that a person may be susceptible to a specific kind of cancer, while it may encourage positive preventive measures, may also negatively shadow many decisions and activities.

A genetic test result may also be inconclusive meaning no definitive result can be given to the individual or family. This may cause the individual to feel more anxious and frustrated and experience psychological difficulties.

Prior to undergoing genetic testing, individuals need to learn from the genetic counselor the likelihood that the test could miss a mutation or abnormality.

Normal results

A normal result for chromosome analysis is 46, XX or 46, XY. This means there are 46 chromosomes (including two X chromosomes for a female or one X and one Y for a male) with no structural abnormalities. A normal result for a direct DNA mutation analysis or linkage study is no gene mutation found.

There can be some benefits from genetic testing when the individual tested is not found to carry a genetic mutation. Those who learn with great certainty they are no longer at risk for a genetic disease may choose not to undergo prophylactic therapies and may feel less anxious and relieved.

Abnormal results

An abnormal chromosome analysis report will include the total number of chromosomes and will identify the abnormality found. Tests for gene mutations will report the mutations found.

There are many ethical issues to consider with an abnormal prenatal test result. Many of the diseases tested for during a pregnancy cannot be treated or cured. In addition, some diseases tested for during pregnancy may have a late-onset of symptoms or have minimal effects on the affected individual.

Before making decisions based on an abnormal test result, the person should meet again with a genetic counselor to fully understand the meaning of the results, learn what options are available based on the test result, and what are the risks and benefits of each of those options.

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Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

American College of Medical Genetics. 9650 Rockville Pike, Bethesda, MD 20814-3998. (301) 571-1825. <http://www.faseb.org/genetics/acmg/acmgmenu.htm>

American Society of Human Genetics. 9650 Rockville Pike, Bethesda, MD 20814-3998. (301) 571-1825. <http://www.faseb.org/genetics/ashg/ashgmenu.htm>.

Centers for Disease Control. GDP Office, 4770 Buford Highway NE, Atlanta, GA 30341-3724. (770) 488-3235. <http://www.cdc.gov/genetics>.

March of Dimes Birth Defects Foundation. 1275 Manaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Human Genome Research Institute. The National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892. (301) 496-2433. <http://www.nhgri.nih.gov>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. <http://www.nsgc.org/GeneticCounselingYou.asp>.

OTHER

Blazing a Genetic Trail. Online genetic tutorial. <http://www.hhmi.org/GeneticTrail/>.

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Katherine S. Hunt, MS

Genotype *see* **Genotypes and phenotypes**

Genotype and phenotype

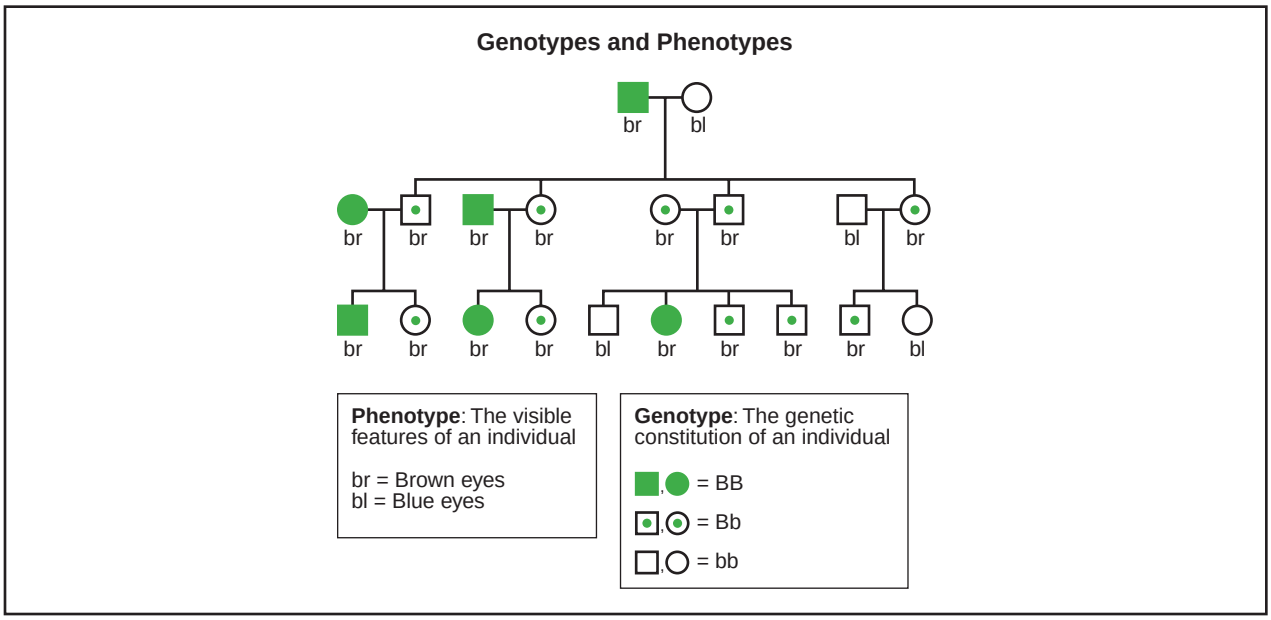
The term genotype describes the actual set (complement) of genes carried by an organism. In contrast, phenotype refers to the observable expression of characters and traits coded for by those genes. Although phenotypes are based upon the content of the underlying genes comprising the genotype, the expression of those genes in observable traits (phenotypic expression) is also, to varying degrees, influenced by environmental factors.

The term genotype was first used by Danish geneticist Wilhelm Johannsen (1857–1927) to describe the entire genetic or hereditary constitution of an organism, In contrast, Johannsen described displayed characters or traits (e.g., anatomical traits, biochemical traits, physiological traits, etc.) as an organism's phenotype.

Genotype and phenotype represent very real differences between genetic composition and expressed form. The genotype is a group of genetic markers that describes the particular forms or variations of genes (alleles) carried by an individual. Accordingly, an individual's genotype includes all the alleles carried by that individual. An individual's genotype, because it includes all of the various alleles carried, determines the range of traits possible (e.g., a individual's potential to be afflicted with a particular disease). In contrast to the possibilities contained within the genotype, the phenotype reflects the manifest expression of those possibilities (potentialities). Phenotypic traits include obvious observable traits as height, weight, eye color, hair color, etc. The presence or absence of a disease, or symptoms related to a particular disease state, is also a phenotypic trait.

A clear example of the relationship between genotype and phenotype exists in cases where there are dominant and recessive alleles for a particular trait. Using an simplified monogenetic (one **gene**, one trait) example, a capital "T" might be used to represent a dominant allele at a particular locus coding for tallness in a particular plant, and the lowercase "t" used to represent the recessive allele coding for shorter plants. Using this notation, a diploid plant will possess one of three genotypes: TT, Tt, or tt (the variation tT is identical to Tt). Although there are three different genotypes, because of the laws governing dominance, the plants will be either be tall or short (two phenotypes). Those plants with a TT or Tt genotype are observed to be tall (phenotypically tall). Only those plants that carry the tt genotype will be observed to be short (phenotypically short).

In humans, there is genotypic sex determination. The genotypic variation in sex **chromosomes**, XX or XY decisively determines whether an individual is female



(Gale Group)

(XX) or male (XY) and this genotypic differentiation results in considerable phenotypic differentiation.

Although the relationships between genetic and environmental influences vary (i.e., the degree to which genes specify phenotype differs from trait to trait), in general, the more complex the biological process or trait, the greater the influence of environmental factors. The genotype almost completely directs certain biological processes. Genotype, for example, strongly determines when a particular tooth develops. How long an individual retains a particular tooth, is to a much greater extent, determined by environmental factors such diet, dental hygiene, etc.

Because it is easier to determine observable phenotypic traits that it is to make an accurate determination of the relevant genotype associated with those traits, scientists and physicians place increasing emphasis on relating (correlating) phenotype with certain genetic markers or genotypes.

There are, of course, variable ranges in the nature of the genotype-environment association. In many cases, genotype-environment interactions do not result in easily predictable phenotypes. In rare cases, the situation can be complicated by a process termed phenocopy where environmental factors produce a particular phenotype that resembles a set of traits coded for by a known genotype not actually carried by the individual. Genotypic frequencies reflect the percentage of various genotypes found within a given group (population) and phenotypic frequencies reflect the percentage of observed expression. Mathematical measures of phenotypic variance reflect the variability of expression of a trait within a population.

The exact relationship between genotype and disease is an area of intense interest to geneticists and physicians and many scientific and clinical studies focus on the relationship between the effects of a genetic changes (e.g., changes caused by mutations) and disease processes. These attempts at genotype/phenotype correlations often require extensive and refined use of statistical analysis.

Antonio Farina, MD, PhD
K. Lee Lerner

Gerstmann-Straussler-Scheinker disease *see* **Prion diseases**

Gestational diabetes *see* **Diabetes mellitus**

Gilles de la Tourette syndrome *see* **Tourette syndrome**

Glanzmann thrombasthemia *see* **Thrombasthenia of Glanzmann and Naegeli**

Glaucoma

Definition

Glaucoma is a group of eye disorders that results in vision loss due to a failure to maintain the normal fluid balance within the eye. If detected in its early stages, vision loss can be prevented through the use of medications or surgical procedures that restore the proper fluid drainage of the eye.

Description

Vision is an important and complex special sense by which the qualities of an object, such as color, shape, and size, are perceived through the detection of light. Light that bounces off an object first passes through the cornea (outer layer) of the eye and then through the pupil and the lens to project onto a layer of cells on the back of the eye called the retina. When the retina is stimulated by light, signals pass through the optic nerve to the brain, resulting in a visual image of an object.

The front chamber of the eye is bathed in a liquid called the aqueous humor. This liquid is produced by a nearby structure called the ciliary body and is moved out of the eye into the bloodstream by a system of drainage canals known as the trabecular meshwork. The proper amount of fluid within the chamber is maintained by a balance between fluid production by the ciliary body and fluid drainage through the trabecular meshwork. When fluid accumulates in the front chamber, either because of an overproduction of fluid or because of a failure of the normal drainage routes, fluid pressure builds up within the eye. Over time, this increased fluid pressure causes damage to the optic nerve, resulting in progressive visual impairment. The condition of increased eye fluid pressure leading to vision loss is known as glaucoma.

Glaucoma is actually a group of many different eye disorders and can manifest alone or as a sign of over 60 different diseases, or even in a healthy person who has experienced an injury to the eye. Physicians classify glaucoma by the type of abnormality in the drainage system. When the drainage passage is narrowed, but still open, it is termed open-angle glaucoma. If the drainage passage is completely blocked, it is termed closed-angle glaucoma. Glaucoma can also be classified by the age of the affected individual: infantile or congenital glaucoma affects infants at birth or children up to three years old, juvenile glaucoma affects individuals from three to 30 years old, and adult glaucoma affects people greater than 30 years old.

Genetic profile

As stated above, there are different forms of glaucoma that either occur alone or as the result of a genetic syndrome. In some cases, specific genetic abnormalities have been identified, while in other forms, the cause is unknown. The known types of glaucoma and the corresponding genetic defect are described in the table below. Many forms of glaucoma are not inherited and thus, are not represented in the table.

As illustrated in the table, glaucoma can be inherited in either an autosomal recessive or an autosomal dominant fashion. In autosomal recessive **inheritance**, two abnormal genes are needed to display the disease. A person who carries one abnormal **gene** does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to a child, who must inherit one abnormal gene from each parent to display the disease. Alternatively, in autosomal dominant inheritance, only one abnormal gene is needed to display the disease, and the chance of passing the gene and the disease to offspring is 50%.

Demographics

Glaucoma is the leading cause of preventable blindness in the United States, affecting more than two million Americans, and is the third leading cause of blindness worldwide. The prevalence of glaucoma increases with age, but the eye condition can also be present in infants and young children. The adult types of open-angle glaucoma account for the majority (70%) of glaucoma cases, while the infantile and juvenile types of glaucoma are relatively uncommon.

The types and rates of glaucoma are not distributed equally among different ethnic groups. For example, the prevalence of glaucoma in Caucasians over 70 years old is 3.5%, while the prevalence in African-Americans is 12%. Also, the primary closed-angle type of glaucoma is much more common in people of Asian or Inuit descent. Apart from ethnicity, risk factors for the development of glaucoma include elevated eye pressure, increasing age, diabetes, and presence of glaucoma in a family member.

Signs and symptoms

In the adult and juvenile forms of open-angle glaucoma, vision loss begins at the periphery (outer edges) of the visual field, resulting in tunnel vision. Because the visual loss in not in the individual's central vision, they may not notice this change. However, if the glaucoma is left untreated, loss of vision progresses and the central vision is often affected, sometimes resulting in blindness. The average time from development of high eye fluid pressures to the appearance of visual loss is 18 years in the adult form, but much shorter in the juvenile form.

In contrast to the adult and juvenile forms, congenital or infantile open-angle glaucoma is noted at birth or

TABLE 1

Types of glaucoma and related genetic information

Disorder	Alternative names	Inheritance	Abnormal protein	Abnormal gene	Gene location
Glaucoma 1, open angle, A (GLC1A)	Juvenile onset primary open-angle glaucoma; Hereditary juvenile glaucoma	Autosomal dominant	Trabecular meshwork-induced glucocorticoid response protein (myocilin)	MYOC, (also known as TIGR, GLC1A, JOAG, GPOA)	1q24.3–q25.2;
			Unknown	Unknown	9q34.1
Glaucoma 1, open angle, B (GLC1B)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	2qcen–q13; (additional loci under investigation)
Glaucoma 1, open angle, C (GLC1C)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	3q21–q24
Glaucoma 1, open angle, D (GLC1D)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	8q23
Glaucoma 1, open angle, E (GLC1E)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	10p15–p14
Glaucoma 1, open angle, F (GLC1F)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	7q35–36
Glaucoma 3, primary infantile, A (GLC3A)	Congenital glaucoma; Buphthalmos	Autosomal recessive	Cytochrome P4501B1	CYP1B1	2p22–p21
Glaucoma 3, primary infantile, B (GLC3B)	Congenital glaucoma	Autosomal recessive	Unknown	Unknown	1p36.2–36.1
Iridogoniodysgenesis, type 1 (IRID1)	Iridogoniodysgenesis anomaly; familial glaucomaIridogoniodysplasia	Autosomal dominant	Forkhead Transcription factor	FKHL7	6P25
Iridogoniodysgenesis, type 2 (IRID1)	Iridogoniodysgenesis anomaly; Iris hypoplasia with early-onset glaucoma	Autosomal dominant	Paired-like homeodomain transcription factor-2	PITX2 (also known as; IDG2,RIEG1, RGS, IGDS2)	4q25–q26
Rieger syndrome, type 1 (RIEG1)	Iridogoniodysgenesis with Somatic anomalies	Autosomal dominant	Paired-like homeodomain transcription factor-2	PITX2 (also known as; IDG2,RIEG1, RGS, IGDS2)	4q25–q26
Rieger syndrome, type 2 (RIEG2)	Iridogoniodysgenesis with Somatic anomalies	Autosomal dominant	Unknown	Unknown	13q14
Glaucoma-related pigment dispersion syndrome (GPDS1)	Pigment dispersion syndrome and pigmentary glaucoma	Autosomal dominant	Unknown	Unknown	7q35–q36

within the first three years of life. Symptoms include cloudy corneas, excessive tearing, and sensitivity to light. Because the eye is very flexible in infants, increased fluid pressure may cause bulging of the eye (buphthalmos, or "ox eye"). Children with glaucoma in only one eye are usually diagnosed earlier because a difference in eye size can be noticed. When the disorder affects both eyes, many parents view the large eyes as attractive and do not seek help until other symptoms develop, delaying the diagnosis.

With closed-angle glaucoma, symptoms come on suddenly. People may experience blurred vision, severe pain, headache, sensitivity to light, and nausea. The development of this type of glaucoma is an emergency and requires immediate treatment.

Diagnosis

The diagnosis of glaucoma may be suggested by certain physical findings, especially in infants, but is con-

KEY TERMS

Aqueous humor—A fluid produced by the ciliary body and contained within the front chamber of the eye.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Buphthalmos—A characteristic enlargement of one or both eyes associated with infantile glaucoma.

Ciliary body—A structure within the eye that produces aqueous humor.

Closed-angle glaucoma—An increase in the fluid pressure within the eye due to a complete, and sometimes sudden, blockage of the fluid drainage passages.

Cornea—The transparent structure of the eye over the lens that is continuous with the sclera in forming the outermost protective layer of the eye.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Gonioscope—An instrument used to examine the trabecular meshwork; consists of a magnifier and a lens equipped with mirrors.

Ophthalmologist—A physician specializing in the medical and surgical treatment of eye disorders.

Ophthalmoscope—An instrument, with special lighting, designed to view structures in the back of the eye.

Optic disc—The region where the optic nerve joins the eye, also refered to as the blind spot.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Optometrist—A medical professional who examines and tests the eyes for disease and treats visual disorders by prescribing corrective lenses and/or vision therapy. In many states, optometrists are licensed to use diagnostic and therapeutic drugs to treat certain ocular diseases.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Tonometer—A device used to measure fluid pressures of the eye.

Trabecular meshwork—A sponge-like tissue that drains the aqueous humor from the eye.

firmed by tests with special instruments. Parents may bring their young infant to a physician if they notice signs of infantile glaucoma, such as changes in the eye shape and size. In adults, who do not show obvious signs of glaucoma, the condition is frequently detected by routine screening eye exams and other tests.

Using an ophthalmoscope (a hand-held or machine mounted instrument using a light source), a physician or optometrist will look through the pupil to the back of the eye. There, they may detect characteristic changes in the region where the optic nerve meets the eye, called the optic disk.

In another portion of a routine eye exam, an ophthalmologist or optometrist will measure the fluid pressure of the eye through the use of a special instrument called a tonometer. The test is painless and involves brief contact of a small probe with the surface of the eye. Presence of elevated pressure (more than 21 mm Hg) means that a person is at risk for glaucoma.

Once high pressures or changes in the optic disk are noted, an ophthalmologist can also use a gonioscope (small lens with a reflecting mirror) to inspect the drainage passageways of the eye and determine if they are blocked. Visual field tests (in which a patient indicates whether they can see small flashing lights that are directed in different spots of the patient's visual field) are used as a final indicator for the presence of glaucoma or a measurement of how far glaucoma-related visual loss has progressed.

Treatment and management

Although there is no treatment for the optic nerve injury and vision loss caused by glaucoma, it is possible to prevent further visual loss by lowering eye fluid pressure. In the adult, this is primarily achieved through medications. Medications can reduce eye fluid pressure by either decreasing fluid production or by increasing fluid drainage from the eye, and can be taken by mouth or applied to the eye through drops. The names of different classes of medications used to treat glaucoma include beta-blockers, alpha agonists, carbonic anhydrase inhibitors, and prostaglandin analogues.

For infantile glaucoma, the treatment is primarily surgical. Laser surgery or microsurgery to open the drainage canals can be effective in increasing drainage of eye fluid. Other types of surgery can be performed to reduce the amount of fluid production. Many children require several operations to lower or maintain their eye fluid pressures adequately, and long-term treatment with medications may still be necessary. For closed-angle glaucoma, immediate hospitalization and treatment with medication is required. Once the person's condition has been stabilized, laser surgery is used to create a passageway for fluid drainage.

All individuals with glaucoma should see an ophthalmologist regularly to evaluate progress of the condition and whether it is being adequately treated. Beginning at the age of 40, all people should receive regular screening exams to detect early signs of glaucoma. People with a family history of glaucoma or with diabetes should receive these screening tests beginning in young adulthood.

Prognosis

Since even small amounts of vision loss due to glaucoma cannot be reversed, early detection of the condition through regular eye examinations is critical. If glaucoma is detected early, lifelong medical treatment can halt the progress of the disease and result in relatively normal vision. If left undiagnosed or untreated, many people with glaucoma will progress to blindness.

Closed-angle glaucoma is an emergency and the prognosis depends on how quickly medical attention is obtained and the severity of the attack. If left untreated, the condition can quickly lead to total vision loss in the affected eye.

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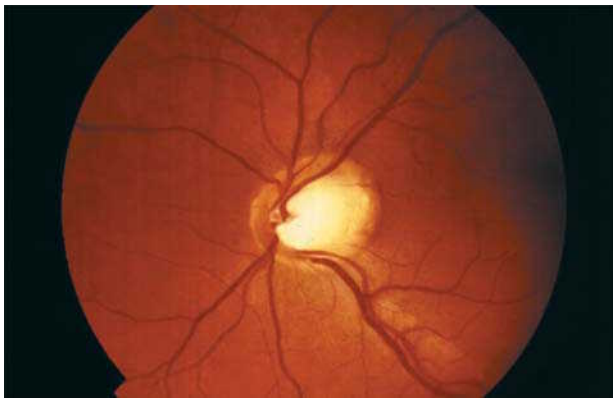
Migdal, C. "Glaucoma Medical Treatment: Philosophy, Principles and Management." *Eye* 14 (June 2000): 515-518.

ORGANIZATIONS

Glaucoma Foundation. 33 Maiden Lane, New York, NY 10038. (800) 452-8266 <http://www.glaucoma-foundation.org>.

Glaucoma Research Foundation. 200 Pine St., Suite 200, San Francisco, CA 94104. (800) 826-6693



Retinal photographs, like the one shown here, can be used to check for signs of glaucoma, such as increased fluid and damage to the optic nerve. *(Custom Medical Stock Photo, Inc.)*

WEBSITES

"Glaucoma." *Online Mendelian Inheritance in Man.* National Center for Biotechnology Information, National Center for Biotechnology Information, National Library of Medicine. Building 38A, Room 8N805, Bethesda, MD 20894. <http://www3.ncbi.nlm.nih.gov/htbin-post/Omim>

Glaucoma Resources on the Internet. <http://www.healthcyclopedia.com/glaucoma.html>.

Oren Traub, MD, PhD

GLB1 deficiency *see* **GM1 gangliosidosis**

Globoid cell leukodystrophy (GCL) *see* **Krabbe disease**

Glucocerebrosidase deficiency *see* **Gaucher disease**

Glycogen storage disease II *see* **Acid maltase deficiency**

GM1-gangliosidosis

Definition

GM1-gangliosidosis is a lysosomal storage condition caused by a reduction or the absence in the amount of the enzyme, beta-galactosidase, in cells. This condition has been referred to by other names such as Norman-Landing disease, Gangliosidosis-GM1 beta-galactosidase-1 deficiency, Hurler-variant, pseudo-Hurler disease, Tay-

Sachs disease with visceral involvement, and GLB1 deficiency.

Description

Lysosomes are structures found inside cells that contain specific proteins and enzymes that help digest or breakdown many of the complex biological substances found within the cells. After the lysosomes digest these substances, the remnants are then released from the cell. The role of the lysosome is to keep the inside of the cell clean and to help the cell function normally.

One of the lysosomal enzymes, beta-galactosidase, is necessary to digest a substance called GM1-ganglioside. When there is not enough beta-galactosidase within the lysosomes, GM1-ganglioside breaks down at a slower rate or not at all. Since GM1-ganglioside is not being digested as fast as it is being produced, GM1-ganglioside accumulates within the lysosomes. When too much GM1-ganglioside accumulates, the lysosomes stop functioning effectively, thereby causing the cell not to function properly.

When there are enough cells in an organ or organ system that stop functioning normally, the entire organ or organ system begins to experience problems. One of the first areas where GM1-ganglioside accumulates and causes problems is within the central nervous system. Other organs and systems in the body can also accumulate GM1-ganglioside; however, signs of the excessive accumulation are sometimes not immediately apparent.

There are three types of GM1-gangliosidoses; they are grouped according to the amount of beta-galactosidase detected in the individual's leukocytes (white blood cells) or skin cells, the individual's age when they start to show symptoms (called age of onset), and the specific symptoms that the individual exhibits. These types are labeled Type I, Type II, and Type III.

Genetic profile

All three types of GM1-gangliosidosis are inherited in an autosomal recessive manner. Symptoms of GM1-gangliosidosis occur when the pair of genes that produce beta-galactosidase (called GLB1) both contain a change, causing them not to work properly. When the GLB1 genes do not work properly, less or no beta-galactosidase is produced. Individuals with GM1-gangliosidosis inherit one of their non-working GLB1 genes from their mother and the other non-working GLB1 **gene** from their father. These parents are called carriers of GM1-gangliosidosis. When two people are known carriers for an autosomal recessive condition, like GM1-gangliosidosis, they have a 25% chance with each pregnancy to have a child affected with the disease.

The GLB1 gene is located on the short arm of chromosome 3, called 3p, in the region 21.33. This is written as 3p21.33. There have been over 20 mutations identified in the GLB1 gene that can cause the gene not to work properly. The most common type of mutation detected is a missense mutation. Typically, a gene is made up of **DNA** that codes for specific amino acids. It is the amino acids, when combined, that make a protein. When there is a missense mutation in a gene, the DNA code for a particular amino acid has been changed, often coding for a different amino acid. Changing the amino acid often changes the protein that is made. A change in the structure or production of a protein often alters its ability to function properly.

Most individuals with GM1-gangliosidosis are compound heterozygotes. This means that an individual with GM1-gangliosidosis has one GLB1 gene containing one mutation and his or her other GLB1 gene has a different mutation. Researchers do not believe that there is any correlation between specific mutations in the GLB1 gene and the severity of GM1-gangliosidosis. An exception to this is the discovery of mutations in the GLB1 gene that, instead of causing an individual to have GM1-gangliosidosis, cause the individual to have another condition called Morquio syndrome type B.

Demographics

GM1-gangliosidosis is a rare condition. It is estimated that approximately one in 100,000–200,000 live births is affected with this condition. Type I GM1-gangliosidosis is considered to occur more often than the other two types. There has also been an increased number of individuals living in Japan, Brazil, and Maltese Island diagnosed with all types of GM1-gangliosidosis. However, many researchers state that this condition is not more common in individuals of certain ethnic groups, although many of the individuals with Type III GM1-gangliosidosis are Japanese. Additionally, GM1-gangliosidosis occurs with equal frequency in males and females.

Signs and symptoms

GM1-gangliosidosis Type I

Type I GM1-gangliosidosis is also called infantile GM1-gangliosidosis or infantile type, and it is considered the most severe form of GM1-gangliosidosis. Infants with GM1-gangliosidosis Type I tend to have less than 1% of the normal amount of beta-galactosidase in their cells.

Some of the symptoms seen with Type I can be apparent at birth, but all infants with Type I will show

characteristics of the condition before six months of age. All infants with Type I will reach a point where they fail to gain new skills and begin to regress and lose the skills they have learned.

Several of the initial symptoms seen in infants with Type I are caused by the storage of GM1-ganglioside in the cells of the infant's central nervous system. One sign of a problem with the central nervous system seen in some infants with Type I is the infant's inability to eat much food or formula because of a poor appetite and/or difficulties with sucking on a bottle or nipple. As a result, they tend to gain very little weight. Another sign of GM1-ganglioside storage in the central nervous system is muscle problems. Most of these infants will have low muscle tone, called hypotonia. These babies appear "floppy" or "loose". As the disease progresses, the infant presents with other central nervous system problems, such as an exaggerated reaction to sound, atrophy of the optic nerves, their bodies becoming rigid and stiff, developing tight joints (joint contractures), and experiencing seizures. Infants with Type I can also develop brain atrophy and/or areas of decreased amount of white matter in the brain.

In GM1-gangliosidosis Type I, GM1-ganglioside is also stored in the skeleton, causing visible changes on radiographs. Some of the more common bone changes are: differences with their vertebrae causing spine curvature, thicker skull, wider bones and hands, and wide, short fingers. Also, the growth of the bones tends to slow down or stop, causing infants with GM1-gangliosidosis Type I to appear smaller than expected for their age.

Additionally, infants with Type I usually develop certain characteristic facial features. The facial features typically seen in infants with Type I include frontal bossing, ears that are set lower on the head than normal, thicker skin, hair on forehead and neck, an elongated space between the nose and mouth, and an enlarged tongue. Children with these facial changes are often described as appearing "coarse". Coarse facial features can also be seen in infants and children who have other types of storage disorders.

Other characteristics of GM1-gangliosidosis Type 1 include an enlarged spleen and liver (called hepatosplenomegaly), cardiomyopathy (which has only been described in caucasian patients), and an enlargement of the cells in the bone marrow. Additionally, infants with Type I have cherry-red spots in the macula of their retinas, and several develop corneal clouding.

GM1-gangliosidosis Type II

GM1-gangliosidosis Type II is also referred to as the juvenile type. In children with Type II, the amount of

KEY TERMS

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are "essential amino acids" which the body cannot make and must therefore be obtained from food).

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Atrophy—Wasting away of normal tissue or an organ due to degeneration of the cells.

Basal ganglia—A section of the brain responsible for smooth muscular movement.

Cardiomyopathy—A thickening of the heart muscle.

Cytoplasm—The substance within a cell including the organelles and the fluid surrounding the nucleus.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Dystonia—Painful involuntary muscle cramps or spasms.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Frontal bossing—A term used to describe a rounded forehead with a receded hairline.

Gray matter—Areas of the brain and spinal cord that are comprised mostly of unmyelinated nerves.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system, which help them conduct impulses more quickly.

Organelle—Small, sub-cellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

White matter—A substance found in the brain and nervous system that protects nerves and allows messages to be sent to and from to brain to the various parts of the body.

beta-galactosidase in the cells is approximately 1–5% of normal.

There are no symptoms that are specific to GM1-Gangliosidosis Type II. Signs of Type II often appear late in infancy or in early childhood. Although each individual with Type II may present differently, several children with Type II have been reported to have difficulty walking and/or developed seizures. The bone changes seen in Type I may or may not occur in children with Type II. Furthermore, children with Type II do not have macular cherry-red spots, enlarged spleen or liver, or the facial changes.

GM1-gangliosidosis Type III

Individuals with GM1-gangliosidosis Type III are also labeled as having the adult or chronic type of this condition. Individuals with Type III tend to have approximately 10% of the normal amount of beta-galactosidase in their cells. The age when symptoms begin to appear in individuals with Type III is extremely variable. There have been reports of individuals with Type III exhibiting symptoms as early as three years of age to as late as 30 years old. The symptoms slowly worsen over many years.

Individuals with GM1-gangliosidosis Type III tend to experience some symptoms related to the storage of GM1-ganglioside in their central nervous system; however, these symptoms are not as severe as those seen in infants with Type I. The signs of GM1-ganglioside storage can be different in each person affected with the GM1-gangliosidosis Type III, but many individuals with Type III have been reported to have signs of **dystonia**. Other neurological symptoms in Type III can include difficulty or unusual method of walking (ataxia), mild mental delays, and slurred speech. Often the ataxia and slurred speech are some of the first symptoms to appear.

Individuals with Type III also have GM1-ganglioside storage in bone cells, but bone changes are considered milder than those seen in Type I. Often the vertebrae of individuals with Type III tend to have a flattened appearance and/or the presence of other mild vertebral changes. On CT or MRI examinations, mild brain atrophy with signs of storage in the basal ganglia can be present in some individuals with Type III. Also, some individuals with Type III have experienced corneal clouding. However, the macular cherry-red spots, facial changes, and differences in the bones are not seen in individuals with GM1-gangliosidosis Type III.

Diagnosis

The diagnosis of GM1-gangliosidosis in an individual can be made by measuring the amount of beta-galactosidase in either skin cells or in leukocytes. Additionally, prenatal testing to determine if a fetus is affected with GM1-gangliosidosis prior to its delivery can be accomplished by measuring the amount of beta-galactosidase on cultured cells from an **amniocentesis** or chorionic villus sampling (CVS). Amniocentesis is a procedure used to remove some of the fluid, which contains fetal cells, from around the fetus. CVS is used to obtain cells from the placenta. With both of these procedures, the cells collected are stimulated to multiply so that there are enough cells to perform certain analyses, in this case measuring the amount of beta-galactosidase. Both of these procedures have their own risks, benefits, and limitations.

X rays can detect bone changes and organ enlargement. However, in early stages of the condition, bone differences may not have developed or the organs may not yet be enlarged. Also, a CT scan and/or MRI can identify brain changes, such as cerebral atrophy or a loss of myelin in the white matter of the brain. An eye examination can detect any macular cherry-red spots or other changes.

Analysis of the amount of beta-galactosidase in an individual's cells cannot be used to determine if the person is a carrier of GM1-gangliosidosis. This is because the range for the amount of beta-galactosidase seen in carriers of this condition overlaps with the range of the amount of beta-galactosidase seen in individuals who are not carriers.

Treatment and management

There is no cure for GM1-gangliosidosis. Most of the treatments revolve around trying to alleviate some of the symptoms, such as helping infants with Type I to eat and devices that can help with problems walking in individuals with Type III. Additionally, there is ongoing research into **gene therapy** for GM1-gangliosidosis to infuse genes that produce beta-galactosidase into the body.

Prognosis

In Type I GM1-gangliosidosis, the child dies within a few years after the symptoms begin, typically by age two. In Type II GM1-gangliosidosis, the prognosis is variable. Some individuals have died during childhood and others have lived many years after symptoms began. In Type III GM1-gangliosidosis, no decrease in lifespan has been reported.

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Sharon A. Aufox, MS, CGC

Goiter-sensorineural deafness syndrome *see* **Pendred syndrome**

Golabi-Rosen syndrome *see* **Simpson-Golabi-Behmel syndrome**

Goldberg syndrome *see* **Neuraminidase deficiency with beta-galactosidase deficiency**

Goldenhar syndrome

Definition

Goldenhar syndrome is a congenital condition that is associated with abnormalities of the head and the bones of the spinal column. The abnormalities of the head can include differences with the eyes, ears, facial bones, and mouth. These differences are extremely variable in severity. The exact cause of Goldenhar syndrome remains unknown.

Description

Goldenhar syndrome was first described by Dr. Maurice Goldenhar in 1952. Individuals with Goldenhar syndrome have physical differences that are present at birth (congenital). These abnormalities are typically limited to the head and bones of the spinal column (vertebrae) and may be severe or mild. In some cases, the changes are seen on both sides of the face (bilateral). In other cases, the changes are limited to one side of the face (unilateral).

Another name for Goldenhar syndrome is oculo-auriculo-vertebral spectrum. This name describes the common birth defects seen in Goldenhar syndrome. The term *oculo* represents the eye, *auriculo* represents the ear, and *vetebral* stands for the physical problems present in the vertebrae.

In Goldenhar syndrome, the facial bones, including the jaw bones (mandible) and cheek bones (maxilla), can be underdeveloped (hypoplasia). This underdevelopment can be limited to one side of the face. This is called *hemifacial microsomia.* Hemifacial microsomia can occur alone or with Goldenhar syndrome. If an individual has hemifacial microsomia without additional birth defects, Goldenhar syndrome is unlikely. Although this is the case, hemifacial microsomia and Goldenhar syndrome are thought to have similar causes.

Genetic profile

Goldenhar syndrome is caused by a disruption of normal facial development. A baby's face forms very early, normally between the eighth and twelfth weeks of pregnancy. Normal facial development depends on many different tissues growing together. When the movement and development of these tissues is disrupted, the face may have abnormal openings, underdevelopment, and/or excess skin.

The exact cause of Goldenhar syndrome is unknown. There are most likely many factors that lead to the abnormal development of the facial tissues. In some cases the factors may be environmental. For example, there are certain medications a woman can take while pregnant that can cause the baby to have the symptoms of Goldenhar syndrome. However, in the vast majority of cases, Goldenhar syndrome is not caused by something taken during pregnancy.

In other cases, normal development of the facial tissues may be disrupted by genetic factors. The exact genetic factors are unknown. Unlike some other syndromes, there has not been a **gene** identified that, if changed, causes Goldenhar syndrome. A few families in which Goldenhar syndrome occurs show an autosomal recessive **inheritance** pattern, while other families clearly support an autosomal dominant pattern of inheritance. However, most cases of Goldenhar syndrome are not inherited, meaning that it does not normally run in families.

Goldenhar syndrome typically occurs randomly. Doctors are often unable to explain why it occurs. Since it is sporadic in nature, if a child is diagnosed with Goldenhar syndrome, the risk for the parents to have another child with Goldenhar syndrome is low. In rare

KEY TERMS

Anopthalmia—A medical condition in which one eye is missing.

Anotia—Absence of an ear.

Auriculo—Related to the ear.

Bilateral—Relating to or affecting both sides of the body or both of a pair of organs.

Cleft lip—A separation of the upper lip that is present from birth but originates early in fetal development. A cleft lip may appear on one side (unilateral) or both sides (bilateral) and is occasionally accompanied by a cleft palate. Surgery is needed to completely repair cleft lip.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Coloboma—A birth defect in which part of the eye does not form completely.

Congenital—Refers to a disorder which is present at birth.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Ear tags—Excess pieces of skin on the outside of the ear.

Epibulbar dermoids—Cysts on the eyeball.

Facial asymmetry—Term used to describe when one side of the face appears different than the other.

Hemifacial microsomia—Term used to describe when one side of the face is smaller than the other.

Hemivertebra—A defect in which one side or half of a vertebra fails to form.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Macrostomia—A mouth that is larger or wider than normal.

Malar hypolplasia—Small or underdeveloped cheekbones.

Mandible—Lower jaw bone.

Mandibular hypoplasia—Underdevelopment of the jaw.

Maxiallary hypoplasia—Underdevelopment of the jaw.

Maxilla—One of the bones of the face.

Microphthalmia—Small or underdeveloped eyes.

Microtia—Small or underdeveloped ears.

Oculo—Related to the eye.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Strabismus—An improper muscle balance of the ocular musles resulting in crossed or divergent eyes.

Unilateral—Refers to one side of the body or only one organ in a pair.

Vertebra—One of the 23 bones which comprise the spine. *Vertebrae* is the plural form.

Vertebral—Related to the vertebrae.

cases, one parent may have some of the physical symptoms of Goldenhar syndrome. If this is the case, the risk to have a child with the disorder may be much higher.

Demographics

Goldenhar syndrome occurs in one of every 3,000 to 5,000 live births. Males are affected more frequently than females. This syndrome is seen in all ethnic groups and cultures.

Signs and symptoms

The abnormalities seen in Goldenhar syndrome are typically limited to the face and vertebrae. Thirty percent of patients have bilateral facial abnormalities. In these patients, the right side is usually affected more severely.

The symptoms associated with Goldenhar syndrome are highly variable. Some individuals with Goldenhar syndrome have many severe abnormalities, while other individuals have few minor birth defects.

Hemifacial microsomia is a common physical difference seen in Goldenhar syndrome. This is caused by hypoplasia (underdevelopment) of the bones of the face. These bones are called the mandible and the maxilla. In addition to the bones of the face, the muscles of the face can also be underdeveloped. Cleft lip and cleft palate are another facial difference associated with Goldenhar syn-

drome. Cleft lip is an abnormal split or opening in the lip that can extend towards the nose or towards the cheek. Cleft palate is an opening in the roof of the mouth. Individuals with Goldenhar can also have wide mouth (macrostomia).

Birth defects of the eye are common in Goldenhar syndrome. Cysts on the eyeball (epibulbar dermoids) are common, as is micropthalmia (small eye). Some individuals with Goldenhar syndrome have tissue missing from the upper eyelid (**coloboma**). Strabismus (crossing of the eyes) is also prevalent.

Abnormal development of the ears is another characteristic of Goldenhar syndrome. The ears may be smaller than normal (microtia), or absent (anotia). Ear tags (excess pieces of skin) may be seen on the cheek next to the ear and may extend to the corner of the mouth. The shape of the ears may also be unusual. Hearing loss is common in individuals with Goldenhar syndrome.

The vertebral problems seen in Goldenhar syndrome result from incomplete development of the vertebrae. Vertebrae can be incompletely developed (hemivertebrae), absent, or fused. Ribs can also be abnormal. Approximately 50% of individuals with Goldenhar syndrome will have curvature of the spine (**scoliosis**).

Other differences outside of the face and vertebra can occasionally be seen in Goldenhar syndrome. Approximately 15% of individuals with Goldenhar syndrome have developmental delay or mental retardation. The likelihood for mental retardation increases if the individual has micropthalmia. Heart defects and kidney defects can also occur.

Diagnosis

There is not a genetic test that can diagnose Goldenhar syndrome. The diagnosis is made when an individual has the common symptoms associated with the condition. The diagnosis is made by a physician.

Treatment and management

Once a child is diagnosed with Goldenhar syndrome, additional tests should be performed. A hearing evaluation is necessary to determine if there is hearing loss. If hearing loss is evident, the child should be referred to a hearing specialist. Speech therapy may also be helpful. X rays of the spine are recommended to determine if there are vertebral problems, and the severity. Individuals with Goldenhar syndrome should also be regularly evaluated for scoliosis. Renal ultrasounds and ultrasounds of the heart may also be recommended, due to the increased risk for birth defects in these areas. A doctor would make this recommendation. Finally, individuals with Goldenhar syndrome should be evaluated by an eye doctor (ophthalmologist).

Surgery may be required to correct the birth defects seen in Goldenhar syndrome. Surgery to correct the facial birth defects can improve appearance and function.

Prognosis

The prognosis for individuals with Goldenhar syndrome is very good. These individuals typically have a normal life span and normal intelligence.

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Goldenhar Parent Support Network. Attn: Kayci Rush, 3619 Chicago Ave., Minneapolis, MN 55407-2603. (612) 823-3529

Goldenhar Syndrome Research & Information Fund. PO Box 61643, St. Petersburg, FL 33714. (813) 522-5772 <http://www.goldenhar.com>.

Goldenhar Syndrome Support Network 9325 163 St., Edmonton, ALB T5R 2P4. Canada <http://i.am/bbds.page>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Holly Ann Ishmael, MS, CGC

Goltz syndrome

Definition

Goltz syndrome, also known as focal dermal hypoplasia or Goltz-Gorlin syndrome, is a rare form of an abnormal skin condition that is believed to be a dominant, X-linked trait. It is named after R. W. Goltz, who first described this syndrome in 1962.

Description

Goltz syndrome is a genetic condition primarily found in females that affects the appearance and function of the skin. An unrelated syndrome, nevoid basal cell carcinoma syndrome (NBCCS), is also known as Gorlin-Goltz syndrome. NBCCS is a non-sex linked dominant disorder characterized by a predisposition to **cancer**, particularly of the basal cells. Care should be taken not to confuse Gorlin-Goltz syndrome with Goltz, or Goltz-Gorlin, syndrome.

Goltz syndrome has many other synonyms, but it is most often referred to as focal dermal hypoplasia (which can be found in the medical literature abbreviated as FDH, FODH, or DHOF) because of the characteristic, localized (focal) skin (dermal) patches that are thin or absent (hypoplasia). Other synonyms include: combined mesoectodermal **dysplasia**, congenital ectodermal and mesodermal dysplasia, ectodermal and mesodermal dysplasia with osseous involvement, focal dermal hypoplasia syndrome, and focal dermato-phalangeal dysplasia.

Goltz syndrome is part of a larger family of diseases known as the ectodermal dysplasias, or abnormalities of the skin, hair, teeth, and nails. In Goltz syndrome, the skin abnormalities take the form of areas of thin skin (lesions) where the skin is completely absent, or discolored, itchy, or blistered. Hair may also be missing in patches, and the teeth are usually poorly formed. Nails may also be unusual in appearance. In addition to these characteristics of the skin and related organs, Goltz syndrome affected individuals can also have skeletal malformations and eye problems.

The obvious bodily symptoms of Goltz syndrome are the result of improper functioning of the skin, an organ whose multiple functions are often overlooked. The skin consists of two layers, the outer skin (epidermis) and the lower skin (dermis). The epidermis layer protects the body from environmental threats such as temperature variations, bacterial infections, and toxic chemicals. In Goltz syndrome, the epidermis is deformed or completely absent. The dermis layer contains cells, which manufacture the protein collagen. Collagen makes up about one-fourth of all the body's protein and plays a vital role in wound healing, skin and muscle support, and bone formation. In Goltz syndrome, abnormal formation of type IV collagen has been found in the dermis including loose collagen bundles and fibers with loss of regular bands. The importance of collagen for many of the body's tissues explains the varied symptoms of Goltz syndrome, which is observed in parts of the body as different as the bones, skin, hair, and fingernails.

Genetic profile

The locus of the **gene** responsible for Goltz syndrome has been localized to the short arm of the X chromosome at locus Xp22.3. At or near this same locus is the gene responsible for **microphthalmia with linear skin defects** (MLS) and the gene responsible for **Aicardi syndrome**. Because of the relatively low number of males diagnosed with this condition, it is assumed that Goltz syndrome is dominant and X-linked with close to 100% fetal mortality in males. Nearly all of the cases of Goltz syndrome are believed to result from *de novo* mutations (new mutations which occur after conception) since parents of affected individuals have normal **chromosomes**.

Demographics

As of 1998, 150 cases of Goltz syndrome in females and only 11 cases in males were reported in the medical literature. Goltz syndrome is not linked to any particular sub-populations. It appears with equal frequency in all races and across all geographies. Because it is an X-linked dominant condition, it is observed with a much higher frequency in surviving females than it is in surviving males.

Signs and symptoms

Goltz syndrome is characterized by localized areas of malformed skin (skin lesions) that appear underdeveloped, streaked, or absent. The skin of an individual affected with Goltz syndrome may lack color (pigmentation) in the affected areas or, the skin may look streaked with lines (linear pigmentation). The affected areas may look and feel inflamed or irritated in various ways such as by exhibiting itching, blistering, reddening and swelling, and even crusting and bleeding. Fatty deposits (papillomas) are usually present in areas of typically sensitive skin, such as the gums, lips, tongue, armpits, vaginal opening, and the anus. Nodules of yellowish fatty tissue can grow on the affected skin, particularly in skin folds.

People with Goltz syndrome often experience excessive skin growth in the palms of the hands and on the soles of the feet. Because of this overgrowth of skin lay-

ers, increased sweating (hyperhidrosis) is often noticed in these areas. Similarly, because of an undergrowth of skin in other parts of the body, many individuals affected with Goltz syndrome do not sweat normally (hypohidrosis) throughout the rest of their bodies.

Additionally, individuals affected with Goltz syndrome may present patches of hair loss on both their scalps and in their pubic regions. The teeth of Goltz syndrome patients are often malformed, mispositioned, or absent, and cavities are commonplace because of missing or incomplete tooth enamel.

Unusual bone formations are also associated with Goltz syndrome. Missing or extra fingers or toes, webbed fingers or toes, permanently bent fingers or toes, and fusion of bones in the fingers or toes have all been observed in Goltz syndrome. Other skeletal abnormalities such as curvature of the spine, underdevelopment or a protrusion of the lower jaw, and fused vertebrae may also be present.

Individuals diagnosed with Goltz syndrome are likely to exhibit facial asymmetry, underdeveloped ears, wide-set eyes, and a pointed chin. Hearing loss, either developed or from birth, is frequently experienced by individuals affected with Goltz syndrome due to the underdevelopment of the ears. Many eye abnormalities have been seen in those affected with Goltz syndrome. These range from missing eyes (anophthalmia) and incomplete formation of the eye (**coloboma**) to clouding of the cornea, drooping eyelids, and crossed eyes. The mucous membranes of the nose and throat may also be affected. Mental retardation has been observed in some, but not all, cases.

Diagnosis

Goltz syndrome is generally diagnosed by the presence of the characteristic skin abnormalities coupled with the characteristic fatty deposits in the gums, lips, armpits, vagina, or anus. It is distinguished from the other possible ectodermal dysplasias by the lack of pigmentation of the skin in some of the affected areas, the abnormal sweating experienced by those individuals affected, the lack of cysts in the eyes, and the presence of tear ducts. The papillomas in the genital areas are often misdiagnosed as genital warts, but Goltz syndrome patients will test negative for human papillomavirus (HPV), the cause of the common genital wart. Prenatal diagnosis is not yet available, but connection to the Xp22.3 locus makes **genetic testing** for this dominant condition potentially possible. In families with a child affected by Goltz syndrome, a skin test on the parents should be conducted to evaluate the potential risk of a second child being born affected with this syndrome.

KEY TERMS

Anopthalmia—A medical condition in which one eye is missing.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Coloboma—A birth defect in which part of the eye does not form completely.

***de novo* mutation**—Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

Dermis—The layer of skin beneath the epidermis.

Ectodermal dysplasia—A hereditary condition that results in the malformation of the skin, teeth, and hair. It is often associated with malfunctioning or absent sweat glands and/or tear ducts.

Epidermis—The outermost layer of the skin.

Hyperhidrosis—Excessive perspiration that may be either general or localized to a specific area.

Hypohidrosis—Insufficient perspiration or absent perspiration which may be either general or localized to a specific area.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Oligodactyly—The absence of one or more fingers or toes.

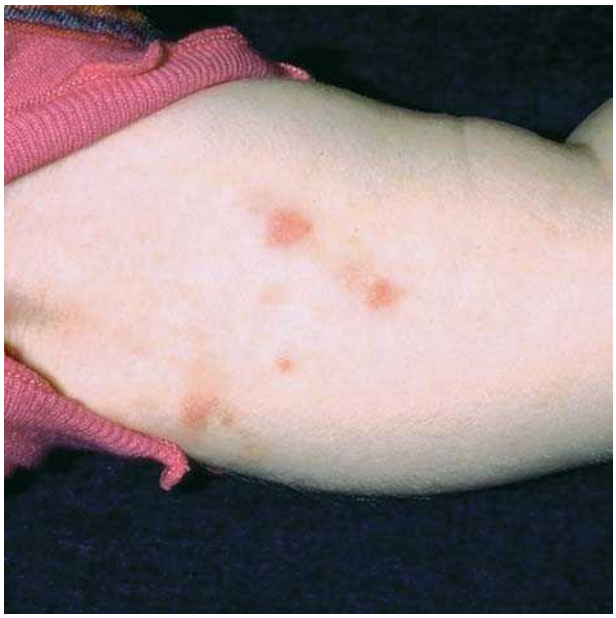
Papilloma—Any benign localized growth of the skin and the linings of the respiratory and digestive tracts. The most common papilloma is the wart.

Treatment and management

The treatment and management of Goltz syndrome varies according to symptoms observed. Dermatological treatments such as skin creams and more targeted treatments are usually indicated. Some affected individuals will require dental work or surgery. Others will need respiratory therapies to keep the nose and throat clear. Certain skeletal deformations seen in Goltz syndrome patients may be corrected by orthopedic surgery. Because of the associated abnormal sweating patterns, those with Goltz syndrome should not be exposed to heat and should avoid heavy exercise.

Prognosis

Goltz syndrome is thought to be almost always lethal in males. Even so, a male patient as old as 68 has been



Papules, small raised sections of skin, such as that shown on this patients arm are characteristic of Goltz syndrome. *(Custom Medical Stock Photo, Inc.)*

reported in the medical literature. In females, a full life expectancy is possible if medical treatment is followed.

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Ectodermal Dyplasia Society. 108 Charlton Lane, Cheltenham, GlosGL53 9EA. UK <http://www.ectodermaldysplasia.org>.

National Foundation for Ectodermal Dysplasias. PO Box 114, 410 E Main, Mascoutah, IL 62258-0114. (618) 566-2020. Fax: (618) 566-4718. <http://www.nfed.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paul A. Johnson

Goltz-Gorlin syndrome *see* **Goltz syndrome**

Goniodysgenesis hypodontia, iridogoniodysgenesis with somatic anomalies *see* **Rieger syndrome**

Goodman syndrome *see* **Carpenter syndrome**

Gordon syndrome *see* **Distal arthrogryposis syndrome**

Greig cephalopolysyndactyly

Definition

Greig cephalopolysyndactyly is a very rare autosomal dominant disorder. The syndrome is characterized by physical abnormalities of the head, face, fingers and toes. Distinct features include extra fingers and/or toes; a large and unusual shape of the skull; a high, prominent forehead; and widely spaced eyes. The range and severity of symptoms may vary greatly between individuals. Some individuals with Greig cephalopolysyndactyly require medical or surgical intervention to manage these problems. The syndrome is familial and in most cases is transmitted as an autosomal dominant trait.

Description

The disorder is named for D. M. Greig (pronounced Gregg), a Scottish physician, who first described the features of this syndrome in 1926. He saw a mother and her daughter who had a peculiar shape of the skull (cephalus) and polysyndactyly of the hands and feet. Polysyndactyly means both extra digits (toes, fingers) as well as webbing (syndactyly) between the digits. Dr. Greig described them as having a high forehead and widely spaced eyes. Thus, the syndrome was termed Greig cephalopolysyndactyly.

Genetic profile

Greig cephalopolysyndactyly (GCPS) can be found in several generations of a family. It is an autosomal

dominant disorder and can be inherited, and passed on, by men as well as women. Almost all genes come in pairs. Cells work best when both copies of the **gene** pairs are intact and do not have mutations. One copy of each pair of genes is inherited from the father, and the other copy of each pair of genes is inherited from the mother. Therefore, if a parent carries a **gene mutation** for GCPS, each of his/her children has a 50% (one in two) chance of inheriting the gene mutation. Each child also has a 50% chance of inheriting the working copy of the gene, in which case they would not have GCPS.

The search to find the causative gene took a number of years. The first clue came in 1989, when an 11-month old infant was found to have a deletion of genetic material on chromosome 7. The infant had a large head and polysyndactyly of the hands and feet. Other reports soon followed, with small deletions and translocations of chromosome 7. Then, in 1991, investigators began to study a gene called GLI-3 as the candidate gene. This gene was found in the region of chromosome 7p13, which was missing in these individuals. The GLI-3 gene was also suspect because of previous studies done in mice.

The mouse gene GLI-3 normally functions in the design of the skeleton and limbs in the embryo. The GLI-3 gene also works in the developing brain. Mice lacking both copies of the gene die before birth. Many have severe birth defects of the brain, skeleton and central nervous system. However, mice with just one non-working copy of the GLI-3 gene do not die. They have minor birth defects, most notably extra digits, often of the hind feet. The mice also have a duplicated bone in their front feet, and an enlarged bone in the front portion of the skull. This combination of birth defects is unusual, but common to both Xt mice and individuals with Greig cephalopolysyndactyly.

With this in mind, the GLI3 gene was scanned for alterations (mutations) in individuals with GCPS. Of interest, both small and large mutations were found throughout the coding gene regions of the gene. As none of these mutations was found in unaffected individuals, this proved that the GLI3 gene was the cause of the condition.

In addition to GSPC, **Pallister-Hall syndrome** and post-axial polydactyly type A (PAP-A), two other disorders of human development, are caused by alterations in the GLI3 gene. The common feature of each disorder is polydactyly of the hands and feet. However, individuals with Pallister-Hall syndrome have additional growth problems and severe mental retardation. Extra fingers and toes are the primary feature of PAP-A, and thus, the most mild in expression of the three conditions.

Scientists have used animal models and the fruit fly *Drosophila* to study the function of the GLI3 gene. The normal function of the GLI3 protein is to bind to the **DNA** helix at specific places. By doing so, it helps to regulate which genes are activated or "turned on." Many of the mutations identified so far seem to interfere with the protein binding function. In effect, other genes that would normally be activated during development of the embryo may in fact not be turned on.

It is known that the limbs (arms, legs, fingers, toes) develop between the fourth and eighth week of pregnancy. The limb defects seen in GCPS must occur during this crucial period of development.

KEY TERMS

Abdominal hernia—Bulging of an organ or tissue through the muscle of the stomach wall.

Chromosome deletion—A missing sequence of DNA or part of a chromosome.

Chromosome translocation—The exchange of genetic material between chromosomes, which can lead to extra or missing genetic material.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Polysyndactyly—Having both extra digits (toes, fingers) as well as webbing (syndactyly) between the digits.

Post-axial polydactyly—An extra finger or toe on the outside of the hand or foot.

Pre-axial polydactyly—An extra finger or toe on the inside of the hand or foot.

Syndactyly—Webbing or fusion between the fingers or toes.

Demographics

Greig cephalopolysyndactyly affects both males and females equally. It most likely occurs in every race and ethnic group. In all, less than 100 individuals have been described worldwide. Therefore, it is a very rare condition.

Signs and symptoms

Most individuals with Greig cephalopolysyndactyly have a large head circumference (the distance as measured around the cranium). The forehead is high and wide, and slightly rounded in front (frontal bossing). This is due to the cranial sutures closing later than normal, causing the bones of the forehead to remain apart. The widen-

ing of the forehead appears to dip down into the space between the eyes, setting the eyes farther apart than normal. The bridge of the nose is broad and flat. This adds to the impression of distance between the eyes. Many times, the rest of the face will also look broad, almost box-like. The chin is small in comparison. The mouth is wide, and the corners of the mouth may be turned downward. The ears are usually normal. Individuals with GCPS can have a short neck, making it look as if the head rests on the shoulders. Intelligence is usually normal, although a few individuals have had mild learning disabilities.

The hands are quite distinctive in appearance. Most individuals with GCPS have extra fingers on each hand. The extra finger is rarely on the thumb side (pre-axial polydactyly). It is most often on the pinky finger side (post-axial polydactyly). Some individuals have an extra finger on each side of the hand, and thus, the possibility of 14 fingers. However, the extra finger may or may not include bone, and could just be a skin tag. The thumbs are frequently quite wide in appearance. Sometimes the bones of the thumb are duplicated or split at the tip. There may also be duplication or fusion in some of the bones that make up the hand, which can be seen on x ray. Their hands are still quite functional, although surgery may be necessary.

Many of these patients will have extra toes. What is unusual is that the extra toe is most often on the great toe side, opposite to what is found in the hands. The toes may also be short. Syndactyly (extensive webbing of the skin) is a constant finding in these patients. The webbing is usually between the toes, but may involve the hands. The webbing can vary from being mild, to complete joining of the digits, with skin up to the nail. Sometimes, just a few of the digits are fused together; in others, all of the toes are webbed. The webbing may also be present alone, without extra toes, although this is uncommon. The syndactyly may also occur on just one foot, and can be quite variable. Foot mobility and walking is usually not a problem.

There are other occasional problems seen in GCPS. These include **craniosynostosis** (premature fusion of the skull bones), mild mental retardation, hernia of the abdominal (stomach) muscles, and lesser birth defects of the urinary tract system, such as hypospadias.

Diagnosis

Each individual with Greig cephalopolysyndactyly is affected somewhat differently. The features are usually quite variable, even within the same family. The facial features can be mild, with most individuals only having a high and broad forehead.

Therefore, the polysyndactyly of the hands and feet remains the most distinctive feature of the syndrome. With the use of x rays, changes in the bones of the hands and feet can be seen. The diagnosis of GCPS is suspected when the physician identifies the extra digits on the outside of the hands and on the inside of the foot, along with the broad forehead. This is usually seen at birth.

The availability of direct gene testing allows for a definitive diagnosis for these patients. Using a blood sample, a direct gene test looking for alterations (mutations) in the GLI3 gene can be done. An identifiable gene mutation would confirm the diagnosis in sporadic (non-inherited) patients as well.

Treatment and management

Very often, the physical characteristics of the face do not require surgical treatment. Sometimes, the facial appearance even improves as the child grows. However, if the cranial sutures in the forehead close either very early or very late, there may be fairly severe disfigurement to the face. This would require surgery from a specialized craniofacial medical team. Craniofacial surgery rearranges or reconstructs the bones of the face to correct the abnormal fusion of the cranial bones.

Some degree of surgery will also be needed for the polydactyly of the hands and feet. The extra digits that are just skin tags (no bone within) are tied off at the base, and allowed to self-amputate. This is usually done at birth. For those digits that include bone, most surgeons would save the digit that would have the best use. The other digit (or digits) would then be surgically removed, usually around one year of age. Surgery is often done to release the webbing of the fingers and toes, and can be quite extensive.

Prognosis

Most individuals with Greig cephalopolysyndactyly appear to have a normal life span.

Resources

ORGANIZATIONS

AboutFace International. 123 Edwards St., Suite 1003, Toronto, ONT M5G 1E2. Canada

FACES: The National Craniofacial Association. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

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Alliance of Genetic Support Groups. <http://www.geneticalliance.org.htm>.

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Kevin M. Sweet, MS, CGC

Griscelli syndrome

Definition

Griscelli syndrome is a rare, sometimes fatal disorder that associates partial **albinism** with immunodeficiency. Partial albinism is characterized by a partial lack of melanin (pigment) in the eyes, hair, and skin. The partial albinism found in patients with Griscelli syndrome is caused by an abnormal melanosome distribution. Immunodeficiency refers to an immune system in which restance to infection is lowered.

Description

In addition to having silvery hair, most people with Griscelli syndrome develop hemophagocytic syndrome, which causes some blood cells in the body to engulf and destroy other blood cells. Hemophagocytic syndrome leads to death unless the patient undergoes a bone marrow transplant.

Some people with Griscelli syndrome are severely impaired neurologically but have no apparent immune abnormalities. Neurologic problems may be spasticity (in which a patient has uncontrolled muscular contractions), rigidity (in which a patient is inflexible or stiff), and convulsions. Through 1994 only 19 patients were reported in the medical literature as having the disorder.

Genetic profile

Griscelli syndrome is an autosomal recessive disorder that sometimes occurs in children with parents who are related by blood. There is evidence that the disorder is caused by mutations in the **gene** that encodes myosin VA, a protein in muscle tissue. (The gene encoding myosin VA is MYO5A.) The gene associated with Griscelli syndrome has been mapped to the long end of chromosome 15 at location 15q21. A second gene, RAB27A, maps very close to the same region (15q21) as MYO5A.

Demographics

Both males and females are born with Griscelli syndrome.

Signs and symptoms

Griscelli syndrome causes pigmentary dilution of the skin and hair, and clumps of pigment in hair shafts. Griscelli syndrome also causes an accumulation of melanosomes in melanocytes.

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Melanin—Pigments normally produced by the body that give color to the skin and hair.

Melanocytes—A cell that can produce melanin.

Melanosomes—Granules of pigment within melanocytes that synthesize melanin.

Peptide—A molecular compound made of two or more amino acids.

Protease—An enzyme that acts as a catalyst in the breakdown of peptide bonds.

People with Griscelli syndrome may also have frequent infections in which pus is present, fever, an abnormal decrease in the number of white blood cells, and a reduction in the number of platelets in the blood.

Diagnosis

Griscelli syndrome can be diagnosed in fetuses in the womb by microscopically examining the hair shaft. After birth, patients are diagnosed with Griscelli syndrome based on the signs and symptoms.

Griscelli syndrome is similar to **Chediak-Higashi syndrome**. For example, both are autosomal recessive disorders in which partial albinism and immunodeficiency are associated. And patients with either disorder are likely to have frequent infections.

However, patients with Chediak-Higashi syndrome are likely to have giant granules in their leukocytes, a type of white blood cell. And leukocyte-specific protease activity is typically low in patients with Chediak-Higashi sydrome, and typically normal in patients with Griscelli syndrome.

Treatment and management

In patients who have hemophagocytic syndrome associated with Gricselli syndrome, treatment may be in the form of bone marrow transplantation.

Prognosis

The prognosis for babies with Griscelli syndrome is poor without bone marrow transplantation.

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Genetic Alliance. 4301 Connecticut Ave.NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937 info@geneticalliance. <http://www.geneticalliance.org>.

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Sonya Kunkle

Gronblad-Strandberg-Touraine syndrome

see **Pseudoxanthoma elasticum**

H

Haim-Munk syndrome

Definition

Haim-Munk syndrome is an extremely rare genetic disorder similar to Papillon-Lefevre syndrome. Features include callous patches of skin on the palms of the hands and the soles of the feet, long pointy fingers, and degeneration of the tissues that surround and support the teeth.

Description

Haim-Munk syndrome is characterized by red, scaly thick patches of skin on the palms of the hands and soles of the feet (palmoplantar hyperkeratosis) that are apparent at birth along with frequent pus-producing (pyogenic) skin infections, overgrowth of the fingernails and toenails (onychogryphosis), and degeneration of the gums and bone surrounding the teeth (periodontosis) beginning in childhood. The severe and ongoing periodontosis usually causes the baby teeth to fall out prematurely, and often results in the loss of the permanent adult teeth as well.

In 1965, researchers Haim and Munk reported findings similar to Papillion-Lefevre syndrome in four siblings from an inbred Jewish family that originated from Cochin, India, on the Malabar Coast and later migrated to Israel. Features that are alike in both Papillion-Lefevre syndrome and Haim-Munk syndrome include skin abnormalities and severe periodontitis. These disorders are considered alternate forms of the same genetic mutation. There are a number of additional features reported in Haim-Munk syndrome that include long, thin, pointed fingers (arachnodactyly), bone loss in the fingers or toes (acroosteolysis), abnormal changes of the nails, and a claw-like deformity of the hands.

Haim-Munk syndrome is also known as Cochin Jewish disorder or congenital keratosis palmoplantaris.

Genetic profile

Haim-Munk syndrome is a homozygous expression of an autosomal recessive trait. Among palmoplantar keratoderma disorders, only Papillon-Lefevre syndrome and Haim-Munk syndrome are associated with the premature loss of teeth. It is suspected that Haim-Munk syndrome could be genetically different from common forms of palmoplantar keratoderma that are linked to the cytokeratin **gene** families.

Preliminary findings suggest that DNA markers other than keratin genes are responsible for the Haim-Munk syndrome. In 1997, genotype data in affected individuals found that the gene mutations in Haim-Munk syndrome were not due to a gene defect in either type I or type II keratin gene clusters on **chromosomes** 12 and 17, markers common to other palmoplantar keratoderma conditions.

Because Papillon-Lefevre syndrome and Haim-Munk syndrome present different symptoms than palmoplantar keratoderma disorders, both genetic syndromes are thought to be related to specific bacterial infections in those with palmoplantar keratoderma.

The cause of Papillon-Lefevre syndrome is a mutation in the cathepsin C gene resulting in periodontal disease and palmoplantar keratosis. Haim-Munk syndrome is thought to be a variant clinical expression of Papillon-Lefevre syndrome that is caused by defects in the cathepsin C gene as well.

A study in 2000 reported a mutation of cathepsin C (exon 6, 2127A→G) that changes a highly conserved amino acid in the cathepsin C peptide. This suggests that Haim-Munk syndrome and Papillon-Lefevre syndrome are alternate forms of defects in the cathepsin C gene. The study also notes that the basis for the difference in clinical expression (symptoms) of these two syndromes caused by the mutated cathepsin C gene is not known.

Demographics

The estimated occurrence of Papillion-Lefevre syndrome, of which Haim-Munk is an extremely rare variant, is considered one to two persons per million. There appears to be no variance by gender. While Papillion-Lefevre syndrome cases have been identified throughout

KEY TERMS

Acroosteolysis—Loss of bone tissue at the ends of the fingers and/or toes.

Arachnodactyly—A condition characterized by abnormally long and slender fingers and toes.

Atrophy—Wasting away of normal tissue or an organ due to degeneration of the cells.

Onychogryphosis—Overgrowth of the fingernails and toenails.

Palmoplantar keratoderma—Group of mostly hereditary disorders characterized by thickening of the corneous layer of skin (hyperkeratosis) on the palms and soles as a result of excessive keratin formation (protein in the skin, hair and nails).

Palmoplantar keratosis—A raised thickening of the outer horney layer of the skin on the palms of the hand and the soles of the feet.

Periodontitis—Inflammatory reaction of the tissues surrounding and supporting the teeth that can progress to bone destruction and abscess formation, and eventual tooth loss.

Pes planus—Flat feet.

Pyogenic—Pus forming.

the world, Haim-Munk syndrome has only been described among descendants of an inbred Jewish family originally from Cochin, India, who migrated to Israel.

Signs and symptoms

The two major manifestations of Haim-Munk syndrome are dermatological abnormalities and juvenile periodontitis.

Individuals identified with the Haim-Munk syndrome show more severe skin abnormalities than groups with Papillion-Lefevre syndrome. Extensive palmoplantar hyperkeratosis typically begins within the first two to three years of life. At birth the palms and soles are bright red in color and then progress to a calloused and scaly appearance. As the patient gets older the disease often involves thick scaly patches on the entire front and back area of the hands and feet, as well as the elbows and knees.

A typical pattern of periodontis with Haim-Munk syndrome is as follows: initially the deciduous (baby) teeth appear at the normal time but the gums proceed to swell and bleed. Usually all the deciduous teeth fall out by age four, the mouth then heals and the secondary teeth begin to appear, severe gingival inflammation develops and the majority, or all, of the permanent teeth often fall out by age 15.

Individuals with Haim-Munk syndrome may also have some of the following signs and symptoms:

- Wasting (atrophy), or thickening, of the nails.
- A deformity of the fingers called arachnodactyly—abnormally long, thin, tapered fingers and toes.
- Lack of normal blood flow to the extremities that results in numbness and tingling in the fingers and/or toes. It also can cause loss of bone tissue at the ends of the fingers and/or toes (acroosteolysis).
- A curve of the bones in the hands causing claw-like features.
- Flat feet (pes planus).
- Recurrent pus-forming (pyogenic) skin infections.

Diagnosis

There are no published diagnostic criteria for Haim-Munk syndrome. Researchers use clinical examination of inbred Jewish Cochin descendents to confirm the presence of Haim-Munk. Diagnosis of Papillon-Lefevre syndrome is confirmed by red, thick calloused skin on the palms and soles at birth and dental problems that are usually present by age five.

Affected individuals are diagnosed with Haim-Munk syndrome when all of the following features are present:

- palmoplantar keratoderma
- thick, rough, and scaly patches of skin on the forearms and legs
- severe early onset periodontitis
- arachnodactyly
- abnormal changes of the nails

Radiology is used to view the thin and tapering bone deformities in the fingers and dental problems associated with Haim-Munk syndrome.

Genetic testing can confirm the mutation of the cathepsin C gene. Genotyping for polymorphic DNA markers (D11S1887, D11S1367, and D11S1367) are used to identify the presence of the cathepsin C gene mutations associated with Haim-Munk syndrome.

Treatment and management

Treatments include extraction of the teeth and use of dental prosthesis, or dentures. Medications are also used to treat skin lesions associated with this disorder.

Prognosis

A normal life span has been reported for individuals with Haim-Munk syndrome. Loss of the baby teeth may occur by age six and loss of the permanent teeth by age 15; however, general health is not impaired and dentures are well tolerated.

Resources

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Nina B. Sherak, MS, CHES

Hair loss syndromes

Definition

Hair loss syndromes are a varied group of disorders and conditions characterized by the gradual or sudden loss of large amounts of hair—most often from the scalp, but sometimes from other areas of the body. Hair loss (or baldness) is sometimes referred to as alopecia. Madarosis is the medical term for the loss of eyelashes (ciliary madarosis) or eyebrows (superciliary madarosis).

Genetic factors are the most common cause of alopecia. Although hair loss, unlike some **genetic disorders**, is not a life-threatening or disabling condition, it often has painful psychological consequences. Good grooming and an attractive appearance are important factors in the contemporary job market as well as interpersonal relationships, and a full head of hair is considered a positive feature. Historically, men have tended to put less weight on their external appearance than women have, but this pattern has changed in the last two decades. Present evidence indicates that men are now as vulnerable to pressures to "look good" as women are, and that hair loss is a frequent focus of men's concerns about their looks. American men spend over two billion dollars each year on hair-replacement products.

Description

Hair loss syndromes can be divided into two major categories, those caused by some type of inflammation, and those caused by genetic factors, aging, or medication side effects. The noninflammatory syndromes are subdivided into two groups according to the pattern of hair loss. The inflammatory syndromes are also subdivided into two groups according to the presence or absence of tissue destruction.

Noninflammatory patterned hair loss

ANDROGENETIC ALOPECIA Androgenetic alopecia is the most common hair loss syndrome, covering about 95% of cases of hair loss. It is also referred to as androgen-dependent or genetic hair loss. In order to understand this form of alopecia, it is useful to begin with some basic facts about the structure and growth cycle of human hair. Hair is composed primarily of keratin, a tough protein that is also found in the fingernails, toenails, and the outermost layer of skin. Each individual hair consists of a hair follicle, which is a small sac that produces the hair shaft, and the hair shaft itself. The average adult scalp contains about 100,000 hair follicles, the number depending on the natural color of the hair. Brunettes have the highest number of scalp follicles (about 155,000), followed by blondes (140,000) and redheads (85,000). The average adult loses between 70 and 100 scalp hairs per day from ordinary combing, brushing, or shampooing. A loss of more than 150 hairs per day is abnormal.

Human hair differs from the hair of other animals in that its growth cycle is not synchronized; an examination of a group of scalp hairs from the same part of the scalp will show that they are in different phases of growth. There are three phases in the human hair growth cycle. Hairs in the anagen, or growth, stage remain in the follicle during an average period of two to eight years, and grow between a quarter-inch and a half-inch per month. About 90% of scalp hairs are in the anagen phase at any one time. At the end of the anagen phase, the hair enters a brief catagen phase lasting between two and four weeks. During this phase the follicle begins to break down. The catagen phase is followed by a telogen, or resting, phase that lasts between two and four months. Hairs in the telogen phase are shed when the growth phase of the next cycle begins and the new hair shaft pushes out the old hair. About 10% of the hairs on the scalp are normally in the telogen phase. These hairs will regrow about six months after they have been shed.

What happens in androgenetic baldness is that the hair growth cycle is affected by the rise in the level of androgens (male sex hormones) in the body that occurs at puberty. Women as well as men produce androgens, although in much smaller amounts. The amount of these hormones does not need to be abnormally high for androgenetic hair loss to occur. Males who have a normal level of androgens and a **gene** for baldness will develop male pattern hair loss, or MPHL. There are two androgens that contribute to MPHL, dihydrotestosterone (DHT) and testosterone. Testosterone is converted to DHT by an enzyme called 5-alpha-reductase. In men with genes for baldness, the hair follicles in the scalp remove testosterone from circulation and convert it to DHT. The action of DHT over time shortens the duration of the anagen phase of the hair growth cycle and decreases the proportion of the hairs in the anagen phase. As the anagen phase decreases, the hairs produced are shorter in length and thinner in diameter. As a larger percentage of the hairs are in the resting or telogen phase, more are lost during normal grooming. This process of the shortening and thinning of each hair shaft is called miniaturization. Miniaturization is accompanied by the loss of hair pigment production, so that the miniaturized hairs are also lighter in color. The light-colored fine hairs that are left at the end of the miniaturization process are called vellus hairs.

In MPHL, hair loss tends to occur in certain areas rather than being distributed evenly over the head. One common pattern is recession of the hair at the temples, with the man's hairline moving backward over time in an "M" pattern. The hair at the crown of the head also begins to thin, and may meet the receding hairline so that the remaining hair forms the rough outline of a horseshoe.

In female pattern hair loss, or FPHL, there is an overall thinning of the hair as well as more pronounced hair loss in certain areas of the scalp, usually the crown. Women with FPHL may find that their hairlines recede a little, but rarely to the same extent as happens in men. Androgens play the same role in hair loss in women that they do in men, since the adrenal glands and ovaries secrete small amounts of androgens.

There are other important differences between FPHL and MPHL:

- FPHL generally appears at later ages, in the woman's late twenties or early thirties, whereas MPHL can affect boys as young as 15.
- FPHL is frequently associated with hormonal changes in women, such as those that occur after childbirth; with the use of birth control pills; or after menopause.
- Women very rarely experience complete loss of hair from a specific area of their scalp due to FPHL. The process of miniaturization in FPHL affects the hair follicles at random, so that some hairs are unaffected. These normal thick hairs are interspersed among thinner, miniaturized hairs.

TRACTION ALOPECIA Traction alopecia is a noninflammatory patterned hair loss syndrome in which the pattern of loss is related to pulling or friction on specific areas of the scalp. It is usually caused either by hair styles in which the hair is pulled into tight braids or held too tightly by rubber bands, or by frequent use of electronic headsets (e.g., Walkman radios, hands-free telephones, etc.) for long periods of time. The tension or rubbing damages the hair shafts and hinders the growth of new hair. In some cases the use of tight hair rollers at night or frequent use of blow dryers on high settings contributes to hair loss from traction alopecia.

TRICHOTILLOMANIA Trichotillomania is a psychiatric disorder that results in patterned hair loss. It is characterized by recurrent episodes of pulling or tugging at the hair in order to relieve stress or tension. The most commonly affected areas are the scalp, the eyebrows, and the eyelashes, although some patients with the disorder pull at hair elsewhere on the body. Trichotillomania can usually be differentiated from other hair loss syndromes by laboratory study of a hair sample.

Noninflammatory diffuse hair loss

TELOGEN EFFLUVIUM Telogen effluvium is a common cause of diffuse hair loss, which means that hairs are shed from all parts of the scalp, not just certain patterned areas. Effluvium is a Latin word that means "outflow," and refers to the large amounts of hair that may be lost. Persons affected by telogen effluvium may lose as much as 30%-40% of their hair in a short period of time.

Telogen effluvium results from an abnormal alteration of the hair growth cycle, in which large numbers of hairs in the anagen phase suddenly switch into the telogen phase. Within six weeks to four months after this switch, these hairs begin to shed.

There are number of possible causes for telogen effluvium, including:

- Major surgery.
- Pregnancy and childbirth.
- Crash dieting.
- Nutritional deficiencies, including iron deficiency.
- Malabsorption syndrome.
- Infectious diseases accompanied by high fever, such as scarlet fever, early syphilis, or typhoid.
- Hypothyroidism.

- Medications. A number of medications are known to cause telogen effluvium, including beta blockers; oral contraceptives; retinoids; nonsteroidal anti-inflammatory agents (NSAIDs), such as indomethacin (Indocin) and ibuprofen (Advil); aspirin and other salicylates; lithium; anticoagulants (blood thinners); and anticonvulsants (medications for seizures).

Telogen effluvium usually stops after a few months and new hair grows in. The first regrowth may be finer than usual but the follicles will eventually produce hair of normal thickness.

ANAGEN EFFLUVIUM Anagen effluvium is a type of diffuse hair loss resulting from a sudden interruption of the growth phase. Unlike the time lag that characterizes telogen effluvium, hair loss in anagen effluvium occurs at once. The most common cause of anagen effluvium is chemotherapy, including treatment with methotrexate, bleomycin, vinblastine, vincristine, cyclophosphamide, doxorubicin, daunorubicin, and cytarabine. This form of hair loss, however, can also be caused by poisoning with arsenic, thallium, bismuth, or borax.

Anagen effluvium usually stops as soon as the chemical cause is removed, but it may take several months for hair to regrow completely.

Inflammatory nonscarring hair loss

ALOPECIA AREATA Alopecia areata is a nonscarring recurrent form of hair loss characterized by smooth round or oval patches of bare skin. There may be some mild itching but no visible skin eruptions. Alopecia areata is usually considered an idiopathic disorder, which means its cause is unknown. Some researchers, however, consider it an autoimmune disorder. It is often triggered by stress or anxiety. Alopecia areata usually affects only the scalp, the eyebrows, and (in men) the beard, but may cause hair loss over the entire scalp (alopecia totalis) or even the entire body (alopecia universalis). The loss of hairs from the eyebrows and eyelashes that may be associated with alopecia totalis is called madarosis.

PSORIASIS Psoriasis is a chronic inflammatory skin disease that frequently affects the elbows and knees as well as the scalp. On the scalp, psoriasis is marked by the appearance of red plaques or patches with silvery scales. These patches may also be found behind the ears. Psoriasis can cause massive but temporary hair loss.

Inflammatory scarring hair loss

In hair loss syndromes marked by tissue scarring, the hair loss is permanent and irreversible. These syndromes should be diagnosed as quickly as possible to minimize the extent of damaged tissue.

LUPUS ERYTHEMATOSUS Lupus erythematosus is an autoimmune disorder than can affect a number of different organ systems. About 85% of lupus patients are women between 20 and 40 years of age. More than 10% of women with lupus develop a form of the disorder known as chronic discoid or chronic cutaneous lupus erythematosus. Chronic discoid lupus can occur on the scalp as well as the face, and is marked by dark red patches or plaques between 0.5 in (1.3 cm) and 0.75 in (1.9 cm) in diameter. The plaques are covered by dry, horny scales that plug the hair follicles and cause permanent hair loss.

LICHEN PLANOPILARIS Lichen planopilaris is a form of lichen planus, an idiopathic recurrent skin disorder that usually affects the wrists, legs, and mucous membranes. It is characterized by itching pinkish-red or purplish patches or pimples on the scalp. Like lupus, lichen planopilaris can cause lasting hair loss.

BACTERIAL OR FUNGAL INFECTIONS Scarring alopecia can be caused by dermatophytes, which are fungi that live on the skin and hair. These fungi include *Trichophyton rubrum*, *Trichophyton tonsurans*, and *Microsporum audouinii*. The dermatophytes infect the skin of the scalp and move down the hair shaft into the follicle, which may be permanently destroyed.

SCLERODERMA **Scleroderma** is a chronic disorder in which the patient's skin and connective tissue become progressively thicker and more rigid. Its cause is not known. As the patient's scalp thickens, the hair is gradually but permanently lost.

INJURIES Scarring alopecia can also result from burns, trauma to the scalp, or radiation treatment.

Genetic profile

Male pattern hair loss (MPHL)

Male pattern hair loss (MPHL) is a polygenic disorder, which means that its appearance is directed by more than one gene. It may be inherited from either the father's or mother's side. The belief that MPHL is inherited only through the mother is a myth. Genes for baldness are, however, dominant, which means that 50% of the children of a balding parent of either sex will inherit the baldness genes. Genetic factors appear to influence the age at onset of MPHL; the extent and speed of hair loss; and the pattern of hair loss. MPHL may begin at any time after the levels of androgens in a boy's blood begin to rise during puberty.

It is important to note that genes for baldness depend on normal levels of androgen in the body to produce androgenetic hair loss. Men who were castrated prior to puberty, or have abnormally low levels of androgen for other reasons, do not go bald even if they have a gene for baldness.

KEY TERMS

Alopecia—Loss of hair or baldness.

Alopecia areata—A nonscarring hair loss syndrome characterized by smooth round or oval hairless areas on the scalp.

Anagen—The growth phase of the human hair growth cycle.

Androgens—A group of steroid hormones that stumulate the development of male sex organs and male secondary sexual characteristics.

Catagen—The breakdown phase of the hair growth cycle.

Dihydrotestosterone (DHT)—A male sex hormone formed from testosterone by the enzyme 5-alpha-reductase. DHT causes hair follicles to shut down, shortening the growth phase of the hair growth cycle and leading to miniaturization.

Effluvium—The medical term for massive hair loss or shedding.

Finasteride—An oral medication used to treat male pattern hair loss. Finasteride, sold under the trade names Proscar and Propecia, is an androgen inhibitor.

Keratin—A tough, nonwater-soluble protein found in the nails, hair, and the outermost layer of skin. Human hair is made up largely of keratin.

Madarosis—The medical term for loss of hair from the eyebrows or eyelashes. Madarosis may be associated with a form of alopecia areata called alopecia totalis. It may also result from such diseases as leprosy and syphilis, or from trauma.

Miniaturization—The process of shortening and thinning of the hair shafts that is found in androgenetic alopecia. It is caused by the effects of DHT on the hair follicle.

Minoxidil—A topical medication sold under the trade name Rogaine for the treatment of male pattern hair loss. It is applied to the scalp as a 2% or 5% solution.

Telogen—The resting phase of the hair growth cycle.

Traction alopecia—Hair loss caused by pressure or tension on the scalp related to certain types of hair styles or equipment worn on the head.

Trichotillomania—A psychiatric disorder characterized by hair loss resulting from compulsive pulling or tugging on one's hair.

Vellus hairs—The fine lighter-colored hairs that result from miniaturization.

Female pattern hair loss (FPHL)

Female pattern hair loss, or FPHL, is also a dominant disorder. At present, however, there is some disagreement as to whether it runs in families to the same extent as MPHL.

Alopecia areata

About 20% of cases of alopecia areata are thought to have a genetic component.

Demographics

Androgenetic alopecia

Androgenetic alopecia is quite widespread in the general United States population. It is estimated that 35 million American men are affected by this hair loss syndrome. About 25% of Caucasian men begin to show signs of baldness by the time they are thirty, and 67% are either bald or developing a balding pattern by age 60. The first evidence of hair loss, namely a receding hair line at the temples, can be found in 96% of Caucasian males over age 15, including those who will not lose any more hair.

There is less agreement on the incidence of androgenetic alopecia among women in the United States; estimates range from 8% to 87%. A commonly accepted figure is that 21 million women are affected. About 80% of girls begin to show some loss of hair at the hairline during puberty, including some who will not develop FPHL.

Alopecia areata

About 2.5 million people in the United States suffer from alopecia areata. It appears to affect men and women equally.

Trichotillomania

Trichotillomania was once thought to be an uncommon disorder, but more recent research suggests that it occurs fairly frequently among adolescents and young adults. Surveys of college students indicate that 1%-2% are or have been affected by trichotillomania. The

male/female ratio is 1:1 in children, but is about 1:4 in college students. The disorder may be underdiagnosed in males because their hair loss is attributed to MPHL.

Signs and symptoms

The signs and symptoms of each hair loss syndrome are included in its description.

Diagnosis

The differential diagnosis of hair loss is usually made on the basis of the patient's history, visual examination of the scalp, and the results of laboratory tests. The more common forms of alopecia can be diagnosed by a family physician, but those that are related to skin disorders may require referral to a dermatologist. There are four key questions that the doctor will ask in evaluating hair loss:

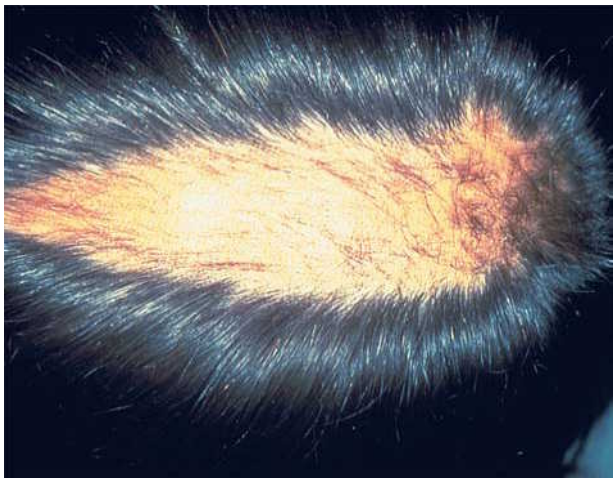
- How long has the patient been losing hair?
- Is there a pattern to the remaining hair?
- Is the hair loss associated with redness, itching, or pain?
- Are there any patches of broken skin, pimples, plaques, or other signs of infection in the affected areas?

Patient history

The patient's medical history may contain information about previous episodes of hair loss; eating and nutritional habits; use of prescription medications; surgery or chemotherapy; occupational exposure to arsenic, thallium, or bismuth; recent illnesses with high fevers; recent periods of severe emotional stress or anxiety; or other factors that may influence hair loss. In addition, the doctor will ask about grooming habits, including the use of dyes, home permanents, hair straighteners, hair sprays, and similar products as well as blow dryers, rollers, and other hair styling equipment.

Laboratory tests

Laboratory tests are performed on samples of the hair itself as part of the differential diagnosis. Microscopic study of a hair sample will indicate, for example, damage to the hair shaft, broken hairs, and changes in the shape of the hair. For example, broken hairs may suggest traction alopecia or trichotillomania. In trichotillomania, there will also be an unusually high number of hairs in the catagen phase. Anagen effluvium produces hairs with tapered or pointed ends, sometimes called "pencil-point" hairs. In telogen effluvium, the hairs have white bulbs at the end and can often be removed from the head by very gentle pulling. In alopecia areata, the area of hair loss is bordered by telltale "exclamation point" hairs.



Alopecia, an inherited hair loss syndrome, results in balding. *(Custom Medical Stock Photo, Inc.)*

Hair samples can also be subjected to chemical analysis if heavy metal poisoning is suspected. Arsenic and thallium are absorbed by the hair shaft and can be detected by appropriate tests.

Skin biopsies are most useful in diagnosis when an infection or other inflammatory condition is suspected as the cause of the hair loss. While scarring can often be seen during a visual examination of the scalp, a biopsy may be the only way to tell if the hair follicles have been destroyed, as well as to differentiate among lupus, dermatophyte infection, alopecia areata, and scleroderma. Biopsies may also be useful in determining the presence of traction alopecia or trichotillomania. In these conditions, pieces of hair shaft are sometimes found in the surrounding skin. Some hair follicles may show signs of injury and are interspersed among normal follicles.

Treatment and management

The treatment of hair loss syndromes is determined by their causes.

Medications

TOPICAL APPLICATIONS Topical applications for hair loss syndromes fall into two major categories—those that stimulate the growth of new hair and those that reduce inflammation. The most frequently prescribed topical medication for male pattern hair loss is minoxidil, which was originally developed to lower high blood pressure. It was approved by the FDA for the treatment of androgenetic hair loss in 1988. Minoxidil, sold under the trade name Rogaine, is applied twice a day as a 2% or 5% solution. Rogaine is also sometimes prescribed for female pattern hair loss and alopecia areata. Its chief drawback

is its high cost—it costs between $650 and $700 a year to use Rogaine twice a day.

Alopecia areata may be treated with topical corticosteroids, or with injections of triamcinolone acetonide (Kenalog) in the affected areas every three or four weeks. Topical corticosteroids are also used to treat chronic discoid lupus, lichen planopilaris, and psoriasis. Tar shampoos are frequently recommended along with topical steroids to treat psoriasis of the scalp.

ORAL MEDICATIONS One oral medication, finasteride, has been approved by the FDA since 1997 for the treatment of male pattern hair loss. Finasteride, sold under the trade names Propecia or Proscar, works by interfering with the body's production of 5-alpha-reductase, the enzyme that converts testosterone to DHT. It is considered the most effective nonsurgical treatment of MPHL. The usual daily dose of finasteride is 1 mg. Unlike minoxidil, finasteride does not appear to be effective in postmenopausal women. It has not been tested on women of childbearing age because its androgen content could cause birth defects in male children.

Oral antifungal medications are considered better than topical preparations for treating dermatophyte infections of the scalp because topical products do not penetrate around the hair follicle. The mostly commonly prescribed oral antifungal drugs are griseofulvin (Grisactin, Fulvicin), ketoconazole (Nizoral), and fluconazole (Diflucan).

Clomipramine (Anafranil), which is a tricyclic antidepressant, or fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI), have been used in the treatment of trichotillomania.

Surgery

As of 2001, surgical transplantation is considered the most effective treatment of MPHL, but is not recommended for alopecia areata. Punch grafts or larger skin flaps bearing the patient's own hair are transferred from areas of the head with normal hair growth to the balding areas. Hair transplantation is expensive but is usually permanent. It appears to work best on patients with dark or curly hair.

Scalp reduction is another surgical technique used in treating MPHL, in which bald areas at the top of the scalp are removed. It works best for patients with relatively little hair loss.

Non-surgical hair additions

These devices consist of human hair, synthetic fibers, or combinations of both. They are added to existing hair or attached to the scalp with adhesives to cover areas of hair loss. They include hair weaves, hair pieces, hair extensions, toupees, partial hair prostheses, and similar devices. Non-surgical hair additions are less expensive than surgery but still cost between $750 and $2500, depending on materials and design. They can be used in combination with hair replacement surgery.

Psychotherapy

Cognitive-behavioral therapy is considered the most effective form of psychotherapy in treating trichotillomania. Individual psychodynamic psychotherapy is often helpful for persons who are emotionally upset by hair loss, particularly those whose employment depends on their appearance.

Prognosis

The prognoses of hair loss syndromes vary according to their causes. Hair loss caused by inflammatory scarring has the worst prognosis, as syndromes or injuries that form scar tissue destroy the hair follicles, preventing regrowth. The prognosis for alopecia areata is less favorable if the disorder affects large areas of the scalp, begins in adolescence, or has existed for a year or longer before the patient seeks treatment. Alopecia areata that begins in adult life and is limited to a few small areas of the scalp often goes away by itself in a few months, although the condition can recur. Diffuse hair loss related to anagen or telogen effluvium has a good prognosis; although complete regrowth may take some months, the hair does come back once the cause is identified and removed.

The prognosis for androgenetic alopecia varies. Rogaine does not work equally well for all men with MHPL. Those who benefit most from treatment with Rogaine have been bald for less than ten years; have a bald spot on the crown of the head that is smaller than 4 inches across; and still have vellus hairs in their balding areas. In addition, hair that grows in as a result of Rogaine will fall out once the patient stops using it. Finasteride is becoming the first-line non-surgical treatment for MPHL because it prevents hair loss as well as aiding regrowth; one study indicates that finasteride prevents further loss of hair in 90% of men even five years after they take it, and assists regrowth in 65% of men even two years later.

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Helm, Thomas N., MD. "Hair Disorders." *Conn's Current Therapy.* Edited by Robert E. Rakel, MD. Philadelphia: W. B. Saunders Company, 2000.

ORGANIZATIONS

American Academy of Dermatology. PO Box 4014, 930 N. Meacham Rd., Schaumburg, IL 60168-4014. (847) 330-0230. Fax: (847) 330-0050. <http://www.aad.org>.

American Hair Loss Council. (888) 873-9719. <http://www.ahlc.org>.

American Society for Dermatologic Surgery. 1567 Maple Ave., Evanston, IL 60201. (708) 869-3954.

Dept. of Health and Human Services. Public Health Service, FDA, 5600 Fishers Lane, Rockville, MD 20857.

National Alopecia Areata Foundation (NAAF). PO Box 150760, San Rafael, CA 94915-0760. (415) 456-4644.

WEBSITES

American Hair Loss Council. <http://www.ahlc.org>.

Food and Drug Administration consumer affairs. <http://vm.cfsan.fda.gov/~dms/cos>.

International Society of Hair Restoration Surgery. <http://www.ishrs.org>.

Rebecca J. Frey, PhD

Hallermann-Streiff syndrome

Definition

Hallermann-Streiff syndrome is a rare genetic condition which causes characteristic facial features, visual abnormalities, tooth problems, short stature, and occasionally mental impairment.

Description

Hallermann-Streiff syndrome is also known as Francois dyscephaly syndrome, Hallermann-Streiff-Francois syndrome, oculomandibulodyscephaly with hypotrichosis, and oculomandibulofacial syndrome. The distinctive facial features of Hallermann-Streiff syndrome include a very small head that is unusually wide with a prominent forehead, a small underdeveloped jaw, an unusually small mouth, and/or a characteristic beak-shaped nose. Small eyes, clouding of the lens of the eyes (cataracts) and other eye problems often leading to blindness are common. Problems with the teeth, skin, hair, and short stature are also common. Most individuals are of normal intelligence but mental impairment has been reported in some. Most cases of Hallermann-Streiff syndrome occur randomly for unknown reasons and may be the result of mutations, or changes to the genetic material.

Genetic profile

Hallermann-Streiff syndrome is a genetic condition. **Genes** are units of hereditary material which are passed to a child by his or her parents. The information contained in genes is responsible for the growth and development of all the cells and tissues of the body. Most genes occur in pairs: one copy of each pair is inherited from the mother through the egg cell and one copy of each pair is inherited from the father through the sperm cell. If there is a gene alteration (mutation), this may interfere with normal growth and development. The specific gene responsible for Hallermann-Streiff syndrome has not yet been identified.

Most cases of Hallermann-Streiff syndrome occur randomly in families with no other affected individuals. In this situation, the gene alteration is a spontaneous mutation. This means that some unknown event has caused the gene (which functions normally in the parent) to change in either the father's sperm or the mother's egg from which the affected individual was conceived. A person who has Hallermann-Streiff syndrome due to a spontaneous mutation can pass on this mutated gene to offspring who will also be affected. The chance for someone with Hallermann-Streiff syndrome to have a child with the same condition is 50% in each pregnancy. There is also a 50% chance to have a child who is not affected with Hallermann-Streiff syndrome.

There are some reports in the literature which indicate that Hallermann-Streiff syndrome is inherited as a recessive condition. Recessive conditions occur when both copies of a gene pair are changed. The affected individual inherits one mutated gene from each parent. The parents of the affected individual are carriers for one changed copy of the gene pair but are not affected themselves. Carrier couples have a 25% chance in each pregnancy to have a child affected with the condition. Diagnosed individuals are at risk to have an affected child only if their partner is also affected or is a carrier. There is no clear agreement on whether Hallermann-Streiff syndrome can be inherited as a recessive condition. Some have argued that the families reported to have recessive Hallermann-Streiff syndrome in fact do not have this condition but some other condition with features very similar to Hallermann-Streiff syndrome.

Demographics

Hallermann-Streiff syndrome affects both males and females in all ethnic groups. There have been over 150 cases reported in the literature.

KEY TERMS

Anesthetic—Drug used to temporarily cause loss of sensation in an area of the body. An anesthetic may either be general, associated with a loss of consciousness, or local, affecting one area only without loss of consciousness. Anesthetics are administered either via inhalation or needle injection.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Trachea—Long tube connecting from the larynx down into the lungs, responsible for passing air.

Tracheostomy—An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Signs and symptoms

Hallermann-Streiff syndrome affects the face, skull, hair, skin, eyes, teeth, and overall growth and development.

Face and skull

The facial features of individuals with Hallermann-Streiff syndrome are distinctive. The face is small with a thin, tapering, pinched nose, and small chin. The head is small and unusually wide with a prominent forehead, a small underdeveloped jaw, and a small mouth. Characteristic changes in the bones of the skull and the long bones of the arms and legs can usually be seen on x ray. The hair is usually sparse, particularly that of the scalp, brows, and lashes. Often there is no hair around the front and sides of the head. The skin of the scalp is thin and taut, and scalp veins are prominent.

Potential complications in Hallermann-Streiff syndrome are related to the narrow upper airway associated with the shape of the skull, particularly the small chin, mouth, and nose. The narrow air passages may result in feeding difficulties and mild aspiration of food. This can lead to severe complications including early lung infection and breathing difficulties. The lung infection can be life-threatening. Some individuals may experience a temporary stop in breathing during sleep because of an obstruction caused by the shape of the skull (obstructive sleep apnea). Individuals with Hallermann-Streiff syndrome are also at increased risk of breathing difficulties when given a general anesthetic before surgery.

Eyes

Individuals with Hallermann-Streiff syndrome may be born with clouding of the lenses of the eyes (congenital cataracts). Congenital cataracts are the most common eye disorder and are usually the reason for a visit to the eye specialist in early life. The cataracts have been reported to spontaneously disappear in some cases. The second most common eye problem is that the eyes are unusually small. Other eye problems may include rapid, involuntary eye movements, crossing of the eyes, and/or decreased visual clarity, and in some cases, blindness.

Teeth

Dental problems are very common. They may include the presence of teeth at birth and the presence of extra teeth. Underdevelopment of tooth enamel and cavities are also common. As well, there may be absence, malformation, and/or improper alignment of certain teeth.

Growth and development

Most individuals with Hallermann-Streiff syndrome are born at term but about one-third are born premature and/or have a low birth weight. Short stature is seen in about half of the individuals with Hallermann-Streiff syndrome. The average final height for females is about 60 in (152 cm) and for males it is about 61 in (155 cm).

Most individuals are of normal intelligence; however, it is estimated that 15-30% of individuals with Hallermann-Streiff syndrome show some degree of mental impairment or slow development. Hyperactivity and seizures have been reported in a small number of individuals.

Other

A small number of individuals with Hallermann-Streiff syndrome have heart defects (such as a hole in the heart). There has also been a report of an individual with a weakened immune system.

Diagnosis

The diagnosis of Hallermann-Streiff syndrome is based on the presence of certain features including the characteristic facial, eye, dental, hair, and skin findings. The main features indicative of Hallermann-Streiff syndrome include a small, wide head with a prominent forehead, the characteristic small jaw and mouth with a pinched nose, cataracts, small eyes, dental abnormalities,

sparse or absent hair, thin skin, and short stature. X rays of the bones of the body may be helpful in establishing a diagnosis of Hallermann-Streiff syndrome because there are characteristic changes evident in the bones of individuals with this condition. There is no laboratory test which can be done to confirm the diagnosis. **Genetic testing** to identify the specific genetic alteration causing the condition is not available since the gene for Hallermann-Streiff syndrome has not been identified. Testing for Hallermann-Streiff syndrome in an unborn baby has not been done. It may be possible to detect the abnormal head shape and small chin on ultrasound (sound wave picture) of the developing baby but this has not been documented in the literature.

Treatment and management

There is no cure for Hallermann-Streiff syndrome. In general, an individual with Hallermann-Streiff syndrome requires a team of specialized doctors for treating the various problems which can occur. Assessments by a dentist, dental surgeon, and oral-facial surgeon may also be necessary to evaluate the teeth and difficulties caused by the small chin and mouth. An assessment for possible airway problems is essential. Any individual with Hallermann-Streiff syndrome who shows signs of day time sleepiness or snoring should be referred to a sleep center for proper diagnosis and treatment of possible obstructive sleep apnea. Treatment for this condition may include surgical procedures such as making a hole in the trachea through the neck to relieve whatever is obstructing the breathing (tracheotomy). Other surgical treatments may include advancing the chin, reducing the size of the tongue, and/or removing the tonsils. Non-surgical treatments may include medications, providing the individual with an oxygen mask, and modifying his or her sleeping position.

An individual with Hallermann-Streiff syndrome should be examined by an eye specialist (ophthalmologist) for signs and symptoms of eye problems. Surgery for some types of eye problems (cataracts, crossed eyes) may be necessary. Individuals who are blind or at risk to lose their eyesight may benefit from being referred to an association for the blind for guidance and counseling.

An examination by a heart specialist (cardiologist) for possible heart problems and by an immune specialist (immunologist) for possible decreased immune function is also recommended. Some types of heart problems may be treated with medications or may require surgical correction.

For individuals with developmental delay or mental impairment, treatment may include special education, speech therapy, occupational therapy, and physical therapy. Drugs may be used to treat hyperactivity, seizures, and other problems.

Some individuals with Hallermann-Streiff syndrome may seek cosmetic surgery for the various effects the syndrome has on the face and skull. Counseling by psychologists may also help individuals with Hallermann-Streiff syndrome cope with the psychological impact of having a facial difference.

Individuals with Hallermann-Streiff syndrome and their families may also benefit from **genetic counseling** for information on the condition and recurrence risks for future pregnancies.

Prognosis

Individuals diagnosed with Hallermann-Streiff syndrome typically have normal intelligence and life-spans when complications of this disorder are properly managed. A major difficulty for individuals with Hallermann-Streiff syndrome is that the visual problems can often lead to blindness, despite surgery. Lung infections can be life-threatening to these patients and must be treated immediately. Breathing problems are another serious complication resulting from the abnormal skull formation that narrows the upper airway. Although uncommon, developmental delay and mental impairment have been reported in a minority of individuals affected with Hallermann-Streiff syndrome. These individuals with significant mental impairment may require life-long supervision.

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ORGANIZATIONS

FACES: The National Craniofacial Association. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

National Eye Institute. 31 Center Dr., Bldg. 31, Room 6A32, MSC 2510, Bethesda, MD 20892-2510. <http://www.nei.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Nada Quercia, Msc, CGC

Hand-foot-uterus syndrome

Definition

Hand-foot-uterus (HFU) syndrome is characterized by abnormalities of the hand, foot, urinary tract, and reproductive tract.

Description

HFU is a rare genetic condition. Its hallmarks include incurving of the fingers (clinodactyly) and shortened and relocated thumbs. There are also wrist- and ankle-bone fusions, very small feet, short great toes, urinary-tract abnormalities, duplications of the reproductive tract in women, urethral openings on the underside of the penis in men, and curved penis. HFU was first described in 1970. Based on the findings of genital abnormalities in affected males, a 1975 study suggested that the more accurate name of the syndrome would be hand-foot-genital (HFG) syndrome.

Genetic profile

The genetic associations of hand-foot-uterus syndrome are not fully understood. A study in 1997 found mutations (changes) in a **gene** called HOXA13, located on chromosome #7, which appears to bring about HFU. It seems that most cases of HFU are caused by a mutation in HOXA13, but other genes may be involved.

Demographics

The ethnic origins of individuals affected by HFU are varied. The syndrome also does not appear to be more common in any specific country.

Signs and symptoms

Signs of HFU syndrome are seen in the hands, feet, urinary tract, and reproductive tract. Individuals in the same family may have different effects of varied severity; this is called intrafamilial variability.

Diagnosis

Diagnosis of HFU is usually made from physical examination by a medical geneticist. Studying x rays of the hands, feet, and reproductive tract also aids in diagnosing the syndrome. Although the HOXA13 gene has clearly been associated with the disease, diagnostic **genetic testing** in affected individuals or in fetuses is not available in 2001.

Treatment and management

There is no specific therapy that removes, cures, or repairs all effects of hand-foot-uterus syndrome. Management of HFU mainly involves the treatment of specific effects. In people with moderate to severe genital, hand, or urinary-tract abnormalities, surgery may be needed.

KEY TERMS

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Prognosis

Since HFU results in a variety of physical signs and symptoms, the prognosis for each affected individual varies. Most people with mild or moderate hand, genital, or foot abnormalities lead normal lives.

Individuals with severe urinary- and/or reproductive-tract abnormalities may require many surgeries. Their prognoses depend on the severity of the abnormalities and survival of the surgeries. Some people with severe reproductive-tract abnormalities may have difficulty having children.

Resources

BOOKS

Children with Hand Differences: A Guide for Families. Center for Limb Differences. Grand Rapids, Michigan: Area Child Amputee Center Publications.

ORGANIZATIONS

Cherub Association of Families & Friends of Limb Disorder Children. 8401 Powers Rd., Batavia, NY 14020. (716) 762-9997.

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Dawn A. Jacob, MS, CGC

HANE *see* **Heredity angioneurotic edema**

Happy puppet syndrome *see* **Angelman syndrome**

HARD + E, Warburg syndrome *see* **Walker-Warburg syndrome**

Harlequin fetus

Definition

The term harlequin fetus is used to describe an extremely severe form of skin disease in which affected infants have thick, plate-like scales all over their bodies. This abnormality is present from birth. It leads to disfiguration of the facial features and limited movement of the arms, legs, fingers, and toes. Most affected infants die during the first several weeks of life, although longer-term survivors have been reported.

Description

Harlequin fetus represents the most severe presentation of inherited ichthyosis. The word **ichthyosis**, which is derived from the Greek word for fish, is a descriptive term used for a group of inherited disorders in which the skin is markedly thickened, ridged, and cracked. The term "harlequin ichthyosis" is therefore used interchangeably with "harlequin fetus." Other synonyms over time have included fetal ichthyosis, ichthyosis intrauterina, keratosis diffusa fetalis, congenital diffuse maligna keratoma, and malignant keratosis.

The ichthyoses as a group are due to a variety of underlying metabolic abnormalities. However, the net effect of each abnormality is the same: keratinization, or differentiation of the cells which make up the skin, does not occur normally. The ichthyoses are separated based on their clinical features and the age at which symptoms appear.

Ichthyosis of the newborn refers to those disorders that present either at birth or shortly thereafter. Each newborn ichthyosis may be due to a different genetic abnormality, even when there is some similarity between clinical features. The harlequin fetus, however, is such a distinct and striking disorder that it is rarely confused with other types of ichthyosis. Affected infants have thick, armor-like skin with deep cracks running in different directions all over their bodies. This gives the appearance of diamond-shaped plaques. The word "harlequin" is often used to describe a variegated pattern, or a combination of patches on a solid background of a contrasting color. The severe skin abnormality leads to an open, fish-mouth appearance as well as a turning outward of the eyelids. Abnormalities of the internal organs are uncommon but have been reported in some individuals. Death often occurs early due to severe skin infection.

Genetic profile

Harlequin fetus (HF) is inherited as an autosomal recessive condition. As such, a child must inherit two copies of the HF **gene** in order to be affected. The presence of one HF gene and one normal gene is consistent with being a gene carrier. Carriers are normal but face a risk of having an affected child with another HF carrier. This risk is 25%, or a one in four chance, that two carriers will each pass on an HF gene to his or her offspring. This risk applies to each pregnancy two carriers have together. Conversely, there is also a 75% chance that two carriers would have an unaffected child.

A gene for harlequin fetus has not yet been identified. It has been speculated that this condition actually represents a varied group of genetic abnormalities, all of which cause a similar clinical picture. This is possible given the number of steps involved in keratinization. If so, it is likely that a different abnormal gene is present in different families.

KEY TERMS

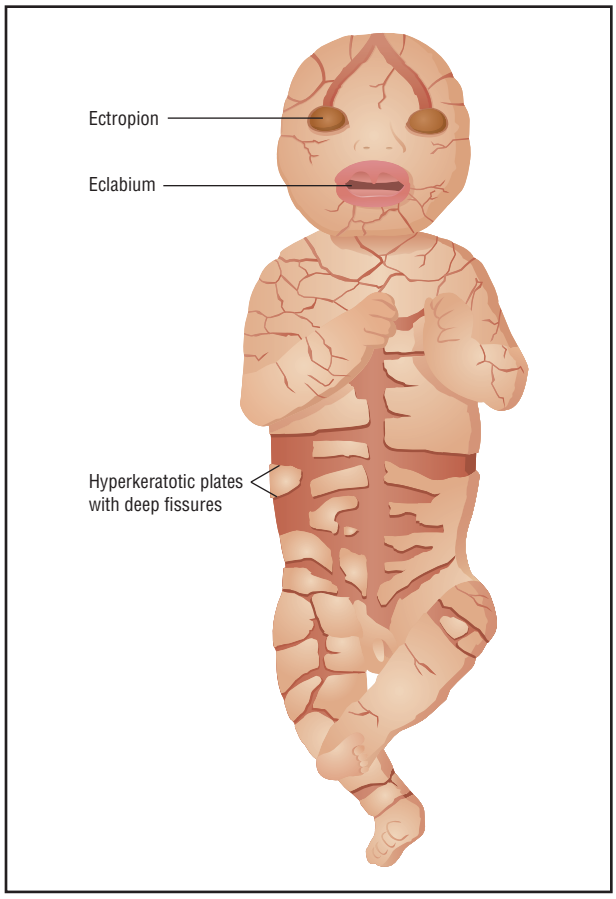
Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Fetoscopy—A technique by which a developing fetus can be viewed directly using a thin, flexible optical device (fetoscope) inserted into the mother's uterus.

Trimester—A three-month period. Human pregnancies are normally divided into three trimesters: first (conception to week 12), second (week 13 to week 24), and third (week 25 until delivery).

Demographics

According to the Foundation for Ichthyosis and Related Skin Types (F.I.R.S.T.), harlequin fetus is a very rare form of congenital ichthyosis. There is limited data available to provide a specific incidence figure. However, F.I.R.S.T. provides one estimate as approximately one in every 200,000 individuals. Like other autosomal recessive conditions, HF has been observed more often among the children of consanguineous, or related, couples, such as first cousins, etc. Biologically related individuals are much more likely to carry the same recessive gene and, hence, have offspring with autosomal recessive disorders. Children with HF have, however, also been born to unrelated parents.



Harlequin fetus is a severe and usually fatal form of ichthyosis. This rare skin disorder results in thick, scaly skin; turning out of the eyelids (ectropion) and the lips (eclabium); and deep skin fissures. *(Gale Group)*

Signs and symptoms

Infants affected with harlequin ichthyosis have a striking and unique appearance at birth. Their skin is unusually thick, off-white in color, with deep, moist cracks running in different directions. The facial appearance is distorted with marked ectropion, or turning outward (eversion) of the eyelids. The lips also appear to be turned outward. This is referred to as eclabium. The external ears are absent or flattened against the side of the head. The hands and feet are also grayish-white in color. The fingers and toes appear malformed, in part due to the thick scale that surrounds them but probably also due to interference with blood flow to the digits from the constrictions. Nails and body hair may be missing. There is limited mobility of arms and legs.

A consistent pattern of associated internal abnormalities has not been identified in infants with HF. However, abnormalities of the central nervous system, kidneys, and lungs have been described in some affected individuals. Short stature has been observed in those infants who have survived the newborn period.

Diagnosis

A diagnosis of HF is possible based on clinical examination after birth. However, in order to confirm a diagnosis of this particular type of ichthyosis, a skin biopsy is strongly recommended. A sample of skin is submitted for electron microscopy. This specific type of technical examination can identify the characteristic changes within the epidermal cells associated with hyperkeratosis, or overgrowth of the stratum corneum. The cells of the stratum corneum contain protein, keratin, and act as a protective barrier along the surface of the body. The process by which new epidermal cells are formed and gradually changed into the cells of the stratum corneum is referred to as keratinization. It is controlled by a number of different metabolic pathways, and an abnormality at any point can theoretically lead to conditions such as ichthyosis or other serious skin abnormalities.

Prenatal diagnosis of harlequin ichthyosis has been accomplished by biopsy of the fetal skin and microscopic analysis of cells from a sample of amniotic fluid. This is usually accomplished by a combination of fetoscopy and **amniocentesis**. The cellular changes associated with hyperkeratosis begin during the latter part of the second trimester of pregnancy. Prenatal diagnosis of HF has been achieved usually around 21-23 weeks gestation. In 1999, a Japanese group was able to successfully diagnosis HF at the earlier gestational age of 19 weeks in an at-risk family.

Realistically, prenatal diagnosis for HF is available only to those couples that have already had at least one affected child. Based on that family history, the parents will be carriers of a gene for HF and thus at 25% risk of having another affected child. Since a gene for HF has not been identified, carrier testing in the general population is not possible. Also, prenatal ultrasound alone will not detect many of the features associated with HF, particularly in a low-risk patient population.

Treatment and management

Infants with HF have a tendency to be born prematurely. Thus, if a prenatal diagnosis of HF has been made, and the family wishes to continue the pregnancy, the woman and her doctor can devise a plan for more intensive monitoring of the remainder of her pregnancy.

Immediate care of a newborn with HF must focus on the following: temperature control, as well as prevention of dehydration, malnutrition, and infection. Infants who are born prematurely may also have breathing problems requiring placement of a breathing tube.

In 1998, guidelines were published for the care of any newborn with a severe form of congenital ichthyosis, including HF:

- The infant should be placed in a humidified incubator immediately after delivery. Antibiotics should be administered via an intravenous (IV) line as a safeguard against infection. An IV should also be used to provide water and nutrients until the infant can suck sufficiently.
- Medication for pain management should be provided, as needed.
- Sponge baths or tub soaking and the application of skin moisturizers with antibiotics should be performed twice a day to soften the skin and reduce scaliness.
- Creams or ointments containing the drug etretinate should be used to decrease the amount of scale. Etretinate has been a successful mode of treatment for some infants with HF, although treated infants still died at relatively young ages due to complications from their disorder. Careful monitoring for etretinate-related side effects in children, such as bone toxicity, is recommended.
- Artifical tear treatments for infants with severe ectropion.

Prognosis

Most infants with harlequin fetus ichthyosis die within the first few days to weeks of life. Common causes of death include respiratory complications because of prematurity or constriction by the thick scale, dehydration, malnutrition, or severe skin infection. Longer-term survivors have been reported but these children have required intensive, on-going medical care. Etretinate has been an effective form of treatment for some infants but its use has only been for short periods of time since the affected infants have still died. Even with treatment, the ichthyosis does not completely go away. However, over time, the eversion of eyelids and lips gradually resolves. Large, thin scales with reddish edges gradually replace the cracked, thick skin. Variable neurological impairment has been reported among survivors, and, even with attentive medical care, sudden death may still occur.

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Pejaver, Ranjan K., et al. "Etretinate in the Management of Harlequin Siblings." *Indian Journal of Pediatrics* 65 (March-April 1998): 320-323.

ORGANIZATIONS

Foundation for Ichthyosis and Related Skin Types. 650 N. Cannon Ave., Suite 17, Landsdale, PA 19446. (215) 631-1411 or (800) 545-3286. Fax: (215) 631-1413. <http://www.scalyskin.org>.

National Registry for Ichthyosis and Related Disorders. University of Washington Dermatology Department, Box 356524, 1959 N.E. Pacific, Rm. BB1353, Seattle, WA 98195-6524. (800) 595-1265 or (206) 616-3179. <http://www.skinregistry.org>.

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"Ichthyosis Congenita, Harlequin Fetus Type." *Online Mendelian Inheritance in Man.* <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=242500>.

Ichthyosis Information. <http://www.ichthyosis.com>.

Terri A. Knutel, MS, CGC

Harlequin ichthyosis *see* **Harlequin fetus**

Haw River syndrome *see* **Dentatorubral-pallidoluysian atrophy**

Heart-hands syndrome *see* **Holt-Oram syndrome**

Hemifacial microsomia with radial defects *see* **Goldenhar syndrome**

Hemihypertrophy (Hemihyperplasia)

Definition

Hemihypertrophy, more correctly termed hemihyperplasia, is defined as the enlargement of one side of the body or part of the body.

KEY TERMS

Congenital—Refers to a disorder which is present at birth.

Hemihyperplasia—A condition in which overdevelopment or excessive growth of one half of a specific organ or body part on only one side of the body occurs.

Hemihypertrophy—Asymmetric overgrowth in which there is an increase in size of existing cells.

Mental retardation—Significant impairment in intellectual function and adaptation in society. Usually associated an intelligence quotient (IQ) below 70.

Prenatal diagnosis—The determination of whether a fetus possesses a disease or disorder while it is still in the womb.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Description

Hemihypertrophy is characterized by unequal (asymmetric) growth of the cranium, face, trunk, limbs, and/or digits. Hemihypertrophy can be an isolated finding, or it can be associated with certain malformation syndromes. Isolated hemihypertrophy refers to hemihypertrophy for which no cause can be found. The degree of asymmetry is variable and very mild cases can go undiagnosed. There are three categories of hemihypertrophy, depending on the body parts involved. The size difference can involve only a specific part of the body such as a finger (called simple hemihypertrophy) or an entire half of the body (called total or complex hemihypertrophy). It usually involves only one side of the body, but can involve both sides (called crossed). There is also hemifacial hyperplasia, which involves one side of the face. Usually multiple organ systems are involved, i.e. the skin, vascular system, internal organs, or bones. In complex hemihypertrophy, the right side is more often involved than the left.

Hemihypertrophy may involve not only the part of the body that is visible, but also the underlying internal organs. Enlargement of one kidney, adrenal gland, testis, and ovary has been reported. The enlarged area usually also has thickened skin, more sebaceous (sweat) glands, more hair, may have pigmentary abnormalities, and the bones may be larger or may be deformed. In persons with facial involvement, the asymmetry can include cheek, lip, nose, ear, eye, tongue, jaw, roof of the mouth, or teeth.

The nervous system may also be affected, causing unilateral nerve enlargement or sciatic nerve inflammation. Occasionally a part of the brain is affected causing mental retardation (15% to 20% of cases). Many cases of hemihypertrophy have hamartomatous lesions (birth marks which involve blood vessels) or abnormalities of the genito-urinary system.

As with other overgrowth syndromes, there is an increased risk for childhood cancers in people with isolated hemihypertrophy (about 6%), particularly cancers of the kidney (Wilms tumor, 3% of individuals), adrenals, and liver.

Genetic profile

The cause and exact mechanism of isolated hemihypertrophy is not known. The asymmetry occurs most likely as a result of an increase in the rate of cell growth, or unregulated cell growth. Most cases of hemihypertrophy are not inherited, but there have been seven familial cases reported as of 2000 in which two or more persons were affected. These cases are not well documented and it is possible that the families actually had another genetic syndrome. Males and females are equally affected with this condition.

It is clear that there is not a single **gene** responsible for hemihypertrophy, but the exact number of genes and their locations and functions are not known. It has been suggested that isolated hemihypertrophy may be related to another condition, called **Beckwith-Wiedemann syndrome**, a genetic overgrowth syndrome that can include both hemihypertrophy and Wilms tumor. Beckwith-Wiedemann syndrome has been associated with abnormalities on chromosome 11, which contains genes involved with growth, development, and **cancer**.

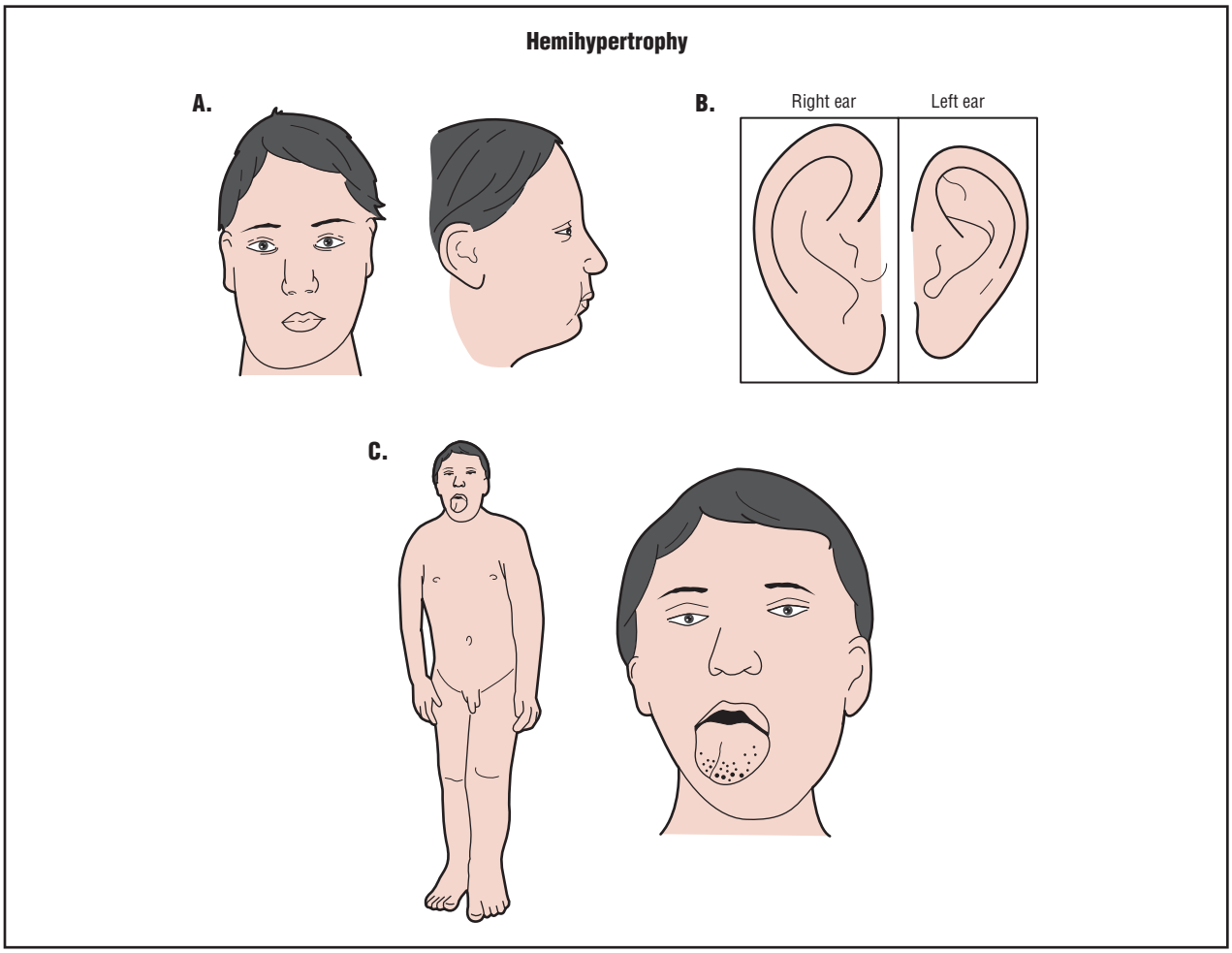
Good data does not exist for recurrence risk for siblings of patients or for children of affected persons. Case reports suggest a slightly increased risk for siblings and for offspring of affected mothers.

Demographics

Hemihypertrophy occurs in about one in 15,000 live births. Isolated hemihypertrophy occurs in about one in 86,000 live births. There are approximately 200 cases reported. Females and males are affected equally.

Signs and symptoms

Hemihypertrophy is usually recognized at birth by physical examination, but can become more serious over



The enlarged growth of only one side of the body is characteristic of hemihypertrophy. The asymetric development may be isolated to one organ or limb, or may occur to the entire body. *(Gale Group)*

time, especially during puberty. Very mild forms of this condition often go unnoticed and are very common.

Diagnosis

The diagnosis is made by clinical examination of body asymmetry. There are no laboratory tests available for this condition. X ray may show advanced bone age or larger bones in the hypertrophied limbs, supporting a diagnosis of hemihypertrophy, or characteristic bone changes supporting another diagnosis. Other genetic syndromes associated with asymmetry must be excluded, as must other causes of asymmetry, such as atrophy of one side of the body due to neurological disorder or skeletal abnormalities that cause asymmetric hand or limb enlargement.

Prenatal diagnosis is theoretically possible by ultrasound, provided that the difference in size is large enough to be detected or if an embryonic tumor is present, although a confirmed diagnosis is not possible until after birth.

Treatment and management

The treatment for hemihypertrophy is different for each individual and depends on the specific symptoms. If leg-length differences are present, corrective shoes can increase the sole for the unaffected leg to prevent **scoliosis** and walking difficulties. Orthopedic devices such as braces or, more rarely, surgery to lengthen the normal leg may be indicated. Surgery to retard growth of the overgrown leg is controversial and not recommended. Surgery for congenital defects or laser surgery for birth marks may be indicated. Plastic surgery may be considered to correct very discrepant facial features.

A protocol to screen for childhood cancers has been proposed, which includes abdominal ultrasound every three months until age six, every six months until puberty, and careful medical follow-up of patients into adulthood. Surgical intervention is appropriate if cancers are detected. Monitoring of serum alpha fetoprotein levels may also be useful as a marker of hepatic tumors.

Appropriate special education services are necessary for those with mental retardation. Counseling related to social stigmatism may be necessary if severe disfigurement is an issue.

Prognosis

Hemihypertrophy does not alter lifespan, although complications from associated abnormalities such as childhood cancer and mental retardation can cause problems. Asymmetry of the limbs can interfere with their proper function and cause pain. Insecurities due to disfigurement are possible and can be addressed through support groups or therapy.

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ORGANIZATIONS

Klippel-Trenaunay Support Group. 5404 Dundee Rd., Edina, MN 55436. (612) 925-2596.

Proteus Syndrome Foundation. 6235 Whetstone Dr., Colorado Springs, CO 80918. (719) 264-8445. abscit@aol.com. <http://www.kumc.edu/gec/support/proteus.html>.

WEBSITES

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National Organization of Rare Disorders. <http://www.rarediseases.org>.

Amy Vance, MS, CGC

Hemochromatosis

Definition

Hemochromatosis is an inherited blood disorder that causes the body to retain excessive amounts of iron. This iron overload can lead to serious health consequences, most notably cirrhosis of the liver.

Description

Hemochromatosis is also known as iron overload, bronze diabetes, hereditary hemochromatosis, and familial hemochromatosis. The inherited disorder causes increased absorption of intestinal iron, well beyond that needed to replace the body's loss of iron. Iron overload diseases afflict as many as 1.5 million persons in the United States. The most common of these, as well as one of the most common **genetic disorders** in the United States, is hereditary hemochromatosis. Men and women are equally affected by hemochromatosis, but women are diagnosed later in life because of blood loss from menstruation and childbirth. It most commonly appears in patients between the ages of 40 to 60 years, since it takes many years for the body to accumulate excessive iron. Symptoms appear later in females than in males—usually after menopause.

Hemochromatosis causes excess iron storage in several organs of the body including the liver, pancreas, endocrine glands, heart, skin, joints, and intestinal lining. The buildup of iron in these organs can lead to serious complications, including heart failure, liver cancer, and cirrhosis of the liver. It is estimated that about 5% of cirrhosis cases are caused by hereditary hemochromatosis.

Idiopathic pulmonary hemosiderosis, a disorder afflicting children and young adults, is a similar overload disorder characterized by abnormal accumulation of hemosiderin. Hemosiderin is a protein found in most tissues, especially the liver. It is produced by digestion of hematin, an iron-related substance.

Genetic profile

Hereditary hemochromatosis is an autosomal recessive condition. This means that individuals with hemochromatosis have inherited an altered (mutated) **gene** from both of their parents. Affected individuals have two abnormal hemochromatosis genes and no normal hemochromatosis gene.

The gene that causes hemochromatosis has been identified, and the most common abnormalities of the gene have been described. The gene is on chromosome 6; it is called HFE. Scientists have not confirmed the function of the normal gene product; they do know that it

interacts with the cell receptor for transferrin. Transferrin binds and transports iron in the blood.

Because it is an autosomal recessive condition, siblings of individuals who have hemochromatosis are at a 25% risk to also be affected. However, the likelihood that an individual will develop symptoms depends on which **gene mutation** he or she has as well as environmental factors. The two most common changes in the HFE gene are C282Y and H63D. The age at which symptoms begin is variable, even within the same family.

Demographics

Hemochromatosis is one of the most common genetic disorders in the United States. Approximately one in nine individuals have one abnormal hemochromatosis gene (11% of the population). Since everyone has two copies of each gene, these individuals have an abnormal HFE gene and a normal gene. They are called carriers. Between 1/200 and 1/400 individuals have two abnormal genes for hemochromatosis and no normal gene.

With most autosomal recessive conditions, an affected person's parents are carriers. If more than one family member has the condition, they are siblings. Hemochromatosis is so common, however, that families are seen in which both parents are affected, or one parent is affected and the other parent is a carrier. More than one generation may be affected, which is not usually seen in rare autosomal recessive conditions.

Signs and symptoms

The symptoms of hemochromatosis include fatigue, weight loss, weakness, shortness of breath, heart palpitations, chronic abdominal pain, and impaired sexual performance. The patient may also show symptoms commonly connected with heart failure, diabetes or cirrhosis of the liver. Changes in the pigment of the skin may appear, such as grayness in certain areas, or a tanned or yellow (jaundice) appearance. The age of onset and initial symptoms vary.

Idiopathic pulmonary hemosiderosis may first, and only, appear as paleness of the skin. Sometimes, the patient will experience spitting of blood from the lungs or bronchial tubes.

Diagnosis

The most common diagnostic methods for hemochromatosis are blood studies of iron, genetic blood studies, magnetic resonance imaging (MRI), and liver biopsy. Blood studies of transferrin–iron saturation and ferritin concentration are often used to screen for iron overload.

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Cirrhosis—A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

Diabetes mellitus—The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

Phlebotomy—The taking of blood from the body through an incision in the vein, usually in the treatment of disease.

Ferritin is a protein that transports iron and liver enzymes. Additional studies are performed to confirm the diagnosis.

Blood studies used to confirm the diagnosis include additional iron studies and/or genetic blood studies. Genetic blood studies became available in the late 1990s. **Genetic testing** is a reliable method of diagnosis. However, in 2001 scientists and physicians studied how accurately having a hemochromatosis mutation predicts whether a person will develop symptoms. Most individuals affected with hemochromatosis (87%) have two identifiable gene mutations, so genetic testing will confirm the diagnosis. Genetic studies are also used to determine whether the affected person's family members are at risk for hemochromatosis. The results of genetic testing are the same whether or not a person has developed symptoms.

MRI scans and/or liver biopsy may be necessary to confirm the diagnosis. MRI studies of the liver (or other iron-absorbing organs), with quantitative assessment of iron concentration, may reveal abnormal iron deposits. For the liver biopsy, a thin needle is inserted into the liver while the patient is under local anesthesia. The needle will extract a small amount of liver tissue, which can be analyzed microscopically to measure its iron content and other signs of hemochromatosis. Diagnosis of idiopathic pulmonary hemosiderosis begins with blood tests and x-ray studies of the chest.

Treatment and management

Patients who show signs of iron overload will often be treated with phlebotomy. Phlebotomy is a procedure

that involves drawing blood from the patient, just like blood donation. Its purpose as a treatment is to rid the body of excess iron storage. Patients may need these procedures one or two times a week for a year or more. Less frequent phlebotomy may be continued in subsequent years to keep excess iron from accumulating. Patients who cannot tolerate phlebotomy due to other medical problems can be treated with Desferal (desferrioxamine). Diet restrictions may also be prescribed to limit the amount of iron ingested. Complications from hemochromatosis, such as cirrhosis or diabetes, may also require treatment. Treatment for idiopathic pulmonary hemosiderosis is based on symptoms.

Diet restrictions may help lower the amount of iron in the body, but do not prevent or treat hemochromatosis. Individuals who are affected or who know they have two C282Y and/or H63D genes may reduce iron intake by avoiding iron and mineral supplements, excess vitamin C, and uncooked seafood. If a patient is symptomatic, he/she may be advised to abstain from drinking alcohol.

Prognosis

With early detection and treatment, the prognosis is usually good. All potential symptoms are prevented if iron levels are kept within the normal range, which is possible if the diagnosis is made before an individual is symptomatic. If a patient is symptomatic but treated successfully before he/she develops liver cirrhosis, the patient's life expectancy is near normal. However, if left untreated, complications may arise which can be fatal. These include **liver cancer**, liver cirrhosis, **diabetes mellitus**, congestive heart failure, and difficulty depleting iron overload through phlebotomy. Liver biopsy can be helpful in determining prognosis of more severely affected individuals. Genetic testing may also be helpful, as variable severity has been noted in patients who have two C282Y genes compared to patients with two H63D genes or one of each. Men are two times more likely than women to develop severe complications. The prognosis for patients with idiopathic pulmonary hemosiderosis is fair, depending on detection and complications.

Prevention

Screening for hemochromatosis is cost effective, particularly for certain groups of people. Relatives of patients with hemochromatosis—including children, siblings, and parents—should be tested by the most appropriate method. The best screening method may be iron and ferritin studies or genetic testing. If the affected person's diagnosis has been confirmed by genetic testing, relatives may have genetic testing to determine whether or not they have the genetic changes present in the affected individual. Many medical groups oppose genetic testing of children. Relatives who are affected but do not have symptoms can reduce iron intake and/or begin phlebotomy prior to the onset of symptoms, possibly preventing ever becoming symptomatic.

Population screening for hereditary hemochromatosis is being widely debated. Many doctors and scientists want population screening because hemochromatosis is easily and cheaply treated, and quite common. Arguments against treatment include the range of symptoms seen (and not seen) with certain gene mutations, and the risk of discrimination in health and life insurance. Whether or not population screening becomes favored by a majority, the publicity is beneficial. Hemochromatosis is a common, easily and effectively treated condition. However, diagnosis may be difficult because the presenting symptoms are the same as those seen with many other medical problems. The screening debate has the positive effect of increasing awareness and suspicion of hemochromatosis. Increased knowledge leads to earlier diagnosis and treatment of symptomatic individuals, and increased testing of their asymptomatic at–risk relatives.

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American Hemochromatosis Society, Inc. 777 E. Atlantic Ave., PMB Z-363, Delray Beach, FL 33483-5352. (561) 266-9037 or (888) 655-IRON (4766). ahs@emi.net. <http://www.americanhs.org>.

American Liver Foundation. 75 Maiden Lane, Suite 603, New York, NY 10038. (800) 465-4837 or (888) 443-7222. <http://www.liverfoundation.org>.

Hemochromatosis Foundation, Inc. PO Box 8569, Albany, NY 12208-0569. (518) 489-0972. s.kleiner@shiva.hunter.cuny.edu. <http://www.hemochromatosis.org>.

Iron Disorders Institute, Inc. PO Box 3021, Greenville, SC 29602. (864) 241-0111. irondis@aol.com. <http://www.irondisorders.org>.

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Michelle Q. Bosworth, MS, CGC

Hemoglobin-beta locus *see* **Beta thalassemia**

Hemolytic-uremic syndrome

Definition

Hemolytic-uremic syndrome (HUS) is a syndrome defined by the presence of acute hemolytic anemia (low red blood cell count caused by the break up of red cells within the blood stream by a person's own immune system), thrombocytopenia (a low number of platelets), and kidney failure. Having these three symptoms all at once can be caused by a number of problems—some by infections, others by genes, and some are still unknown.

Description

About 90% of HUS cases occur in children less than five years of age. In most cases, there is an early phase of diarrhea, followed by the lowered blood counts and the **renal failure**. Most patients get better after HUS, a few die during the worst stage of the illness, others go on to have life-long kidney disease, and some will progress to having a form of HUS that comes and goes over the rest of their lives. Which patients will have which outcome is not known during the illness.

Many infectious organisms have been thought to play a role as things that may cause HUS outbreaks, such as one *E. coli* serotype and one *Shigella dysenteriae* serotype. About 40% of patients who ingest *E. coli* 0157:H7 (the implicated serotype) will go on to get some form of diarrhea. Of those that develop diarrhea, about 5% will progress to some form of HUS (ranging in strength from mild to fatal). The bacteria linked to HUS have been shown to produce a toxin that gets released into the bloodstream after the organisms invade the colon's mucosal lining. The toxin, once inside of cells, disrupts protein synthesis. The spreading of organisms that make toxins tends to occur through food products.

Many outbreaks of HUS in the United States have occurred over the last several decades. These outbreaks have been linked to various food sources such as hamburger meat that is not cooked enough, apple juice and apple cider that has not been pasteurized, water, fruits, vegetables, and unpasteurized milk. Hamburger meat is the most common way that *E. coli* spreads. This bacteria is part of the normal flora of cow intestines and it is thought that it gets into the meat during the process of killing and cutting up the cow. When this beef is then not cooked enough to kill the organism, it is able to travel into the human GI (gastro-intestinal) system with ease. The spreading of this disease can also occur with person-to-person contact through a fecal-oral route. Support for this theory includes data from daycare centers that had outbreaks of HUS.

About 10% of cases in children and 50% of cases in adults will be a type of HUS that occurs without diarrhea. Of these cases, some can be linked with other infections, but other cases have no clear cause. Out of these unclear cases, some will be a form of HUS that runs in families. There have been many research studies into families that have many members who have a form of HUS that keeps coming back over the patient's lifetime. Genetic tests of these families have found what may be a **gene** that can cause some cases of HUS.

Patients with HUS all show signs of making thrombi (blood clots) in small vessels. These thrombi form in kidney blood vessels as well as small arteries all over the body. Thus, clots can cause infarcts (starvation and death) of kidney tissue, brain tissue, the bowel, and other organs.

Genetic profile

While most families that have a form of HUS that passes on the disease in an autosomal recessive pathway, there have been some families with signs of autosomal dominant transmission. Genetic tests have found that a region on chromosome 1q can play a role in the forms of HUS that run in families. The gene for factor H (a protein regulator of the alternate complement pathway) is the leading gene candidate. Molecular proof linking factor H to cases of HUS that occur without diarrhea was first produced in 1998. Since then, screening of patients and families of patients with HUS not linked to a preceding episode of diarrhea have found a subset of patients who have mutated copies of the factor H gene.

KEY TERMS

Alternate complement pathway—A cascade of enzymatic reactions that produce antibacterial proteins. This pathway helps to ward off infections.

Idiopathic—Of unknown origin.

Serotype—One form of a bacteria that has unique surface proteins. Each serotype causes a unique antibody response from a person's immune system.

Tests that look at different families with an inherited form of HUS have shown that there are many different point mutations within the factor H gene. All of these mutations led to some reduced level of factor H. With this lower level, many researchers have noticed that patients also have reduced levels of a protein called C3. This protein is part of the complement cascade that is supposed to attack bacteria within the body. Patients with low levels of C3 may be at more risk of having very bad problems arise from infections than patients with normal immune systems. Also, the familial form of HUS is most likely a multifactorial disease (i.e. no one **gene mutation** causes it by itself) that occurs in certain patients who are predisposed to the disorder.

Demographics

The largest number of cases occur in children between the ages of six months and five years of age. The mean age of children who get HUS is four. Within the United States, this disease most often occurs in epidemics, versus an endemic form that is found in other parts of the world. For example, Argentina has a much higher incidence of HUS than America. Interestingly, the rate of *E. coli* that make the oxins that cause infections is higher in Argentina.

Signs and symptoms

The clinical history most often seen in patients with HUS is of a diarrheal illness that comes before the anemia and renal disease by five to seven days. Some children have symptoms other than diarrhea. These include belly pain, nausea, and throwing up.

When HUS occurs, patients can have many different types of symptoms. Patients tend to have pallor (pale skin), decreased urine output, and fatigue. Even though they tend to have low platelet (the cells that cause blood to clot) counts, they seldom have too much bleeding. About one quarter of patients will have neurologic signs and symptoms that present as seizures, drowsiness, coma, and personality changes. Most of the patients that have HUS with diarrhea will also have hypertension (high blood pressure) that occurs with it. Almost one fifth of patients with HUS will also have some form of pancreatic problems that can lead to the body not making enough insulin and causing diabetes. In some cases, the diabetes may last for the rest of the patient's life.

Kidney problems vary from patient to patient in how severe they may be. Some patients only have lower urine output, but others progress to full kidney failure. In some patients who develop HUS *without* diarrhea, the onset of renal failure will be more subtle such that they will present with symptoms of volume overload (too much retained fluid).

Diagnosis

The diagnosis of HUS should be considered in patients who present with symptoms of anemia or renal failure who either give a history of diarrhea before it or have certain problems that show up in their lab tests. Patients will always have low red blood cell counts (anemia) with signs of the ongoing break down of red blood cells. On peripheral smear (blood looked at through a microscope), Burr cells can be seen. These are red blood cells with bumps sticking out of the surface of the cell. Also schistocytes (pieces of red blood cells that have been destroyed) can be seen under the microscope which provide clues of the ongoing break down of red blood cells (hemolysis).

Diagnosis of familial HUS will depend on the presence of many cases within one family that are not linked to an outside epidemic. Often, the cases will occur over a stretch of many years. As of yet, there is no genetic or lab test that can tell which people will get familial HUS. Prenatal testing is not yet available either.

Treatment and management

There is no certain treatment for patients with HUS other than supportive care. Many types of treatments have been tried in attempts to reduce the amount of clotting that occurs in small vessels, but with little or no success. Antibiotic treatment for children with diarrhea caused by *E. coli* tended to raise, instead of lower, the rate of transformation into HUS. Thus, antibiotics tend to not be used for children with diarrhea. They are of little benefit and may be harmful. Treatment of diarrhea in children should consist of supportive care with ample fluids in order to prevent dehydration.

Careful notice must be paid to fluid intake. It is very easy for kidney failure patients to build up too much volume and have problems with their electrolyte levels.

Patients with really low red blood cell counts can be given blood transfusions. Those who get severe renal failure may need dialysis treatment to rid their blood of toxins that would have been cleared by the kidneys. These treatments apply to all forms of HUS including HUS with diarrhea, HUS without diarrhea, and familial HUS. In some patients with recurring familial disease, kidney transplants have been tried, but the disease did recur in many patients.

Prognosis

About 10% of children will die during the acute phase of the illness or will be left with chronic renal or brain damage. Most of the deaths during the acute phase occur in children where organs other than the kidneys are also involved (i.e. brain thrombi formation). Long term effects also include diabetes, rectal stricture (narrowing of the rectum caused by fibrous tissue formation), and neurologic deficits (related to strokes). Of children who have HUS with diarrhea (most of the cases), about 1% will have the illness return.

In adults, the death rate is much higher, at 15 to 30%. Also, 30% of those who do not die from HUS will have chronic kidney damage and 25% may go on to have the disease recur. This difference in age-related recurrence rates and outcomes may be due to the fact that a higher number of adults get the form of HUS that begins without diarrhea.

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Benjamin Morris Greenberg

Hemophilia

Definition

Hemophilia is a genetic disorder—usually inherited—of the mechanism of blood clotting. Depending on the degree of the disorder present in an individual, excess bleeding may occur only after specific, predictable events (such as surgery, dental procedures, or injury), or occur spontaneously, with no known initiating event.

Description

The normal mechanism for blood clotting is a complex series of events involving the interaction of the injured blood vessel, blood cells (called platelets), and over 20 different proteins which also circulate in the blood.

When a blood vessel is injured in a way that causes bleeding, platelets collect over the injured area, and form a temporary plug to prevent further bleeding. This temporary plug, however, is too disorganized to serve as a long-term solution, so a series of chemical events occur, resulting in the formation of a more reliable plug. The final plug involves tightly woven fibers of a material called fibrin. The production of fibrin requires the interaction of several chemicals, in particular a series of proteins called clotting factors. At least thirteen different clotting factors have been identified.

The clotting cascade, as it is usually called, is the series of events required to form the final fibrin clot. The cascade uses a technique called amplification to rapidly produce the proper sized fibrin clot from the small number of molecules initially activated by the injury.

In hemophilia, certain clotting factors are either decreased in quantity, absent, or improperly formed. Because the clotting cascade uses amplification to rapidly plug up a bleeding area, absence or inactivity of just one clotting factor can greatly increase bleeding time.

Hemophilia A is the most common type of bleeding disorder and involves decreased activity of factor VIII. There are three levels of factor VIII deficiency: severe, moderate, and mild. This classification is based on the percentage of normal factor VIII activity present:

- Individuals with less than 1% of normal factor VIII activity level have severe hemophilia. Half of all people with hemophilia A fall into this category. Such individuals frequently experience spontaneous bleeding, most frequently into their joints, skin, and muscles. Surgery or trauma can result in life-threatening hemorrhage, and must be carefully managed.

KEY TERMS

Amplification—A process by which something is made larger. In clotting, only a very few chemicals are released by the initial injury; they result in a cascade of chemical reactions which produces increasingly larger quantities of different chemicals, resulting in an appropriately-sized, strong fibrin clot.

Factors—Coagulation factors are substances in the blood, such as proteins and minerals, that are necessary for clotting. Each clotting substance is designated with roman numerals I through XIII.

Fibrin—The final substance created through the clotting cascade, which provides a strong, reliable plug to prevent further bleeding from the initial injury.

Hemorrhage—Very severe, massive bleeding that is difficult to control. Hemorrhage can occur in hemophiliacs after what would be a relatively minor injury to a person with normal clotting factors.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

Trauma—Injury.

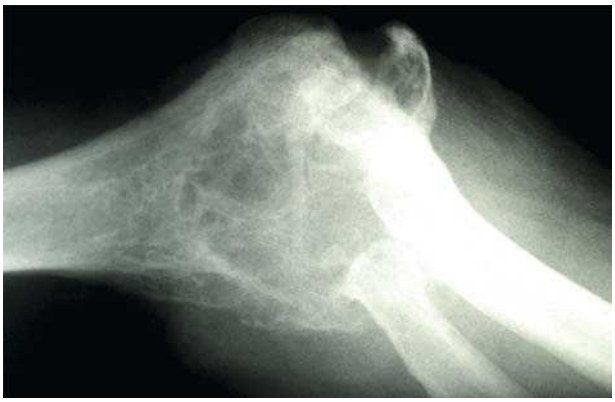
- Individuals with 1–5% of normal factor VIII activity level have moderate hemophilia, and are at risk for heavy bleeding after seemingly minor traumatic injury.
- Individuals with 5–40% of normal factor VIII activity level have mild hemophilia, and must prepare carefully for any surgery or dental procedures.

Individuals with hemophilia B have symptoms very similar to those of hemophilia A, but the deficient factor is factor IX. This type of hemophilia is also known as Christmas disease.

Hemophilia C is very rare, and much more mild than hemophilia A or B; it involves factor XI.

Genetic profile

Hemophilia A and B are both caused by a genetic defect present on the X chromosome. (Hemophilia C is inherited in a different fashion.) About 70% of all people with hemophilia A or B inherited the disease. The other 30% develop from a spontaneous genetic mutation.



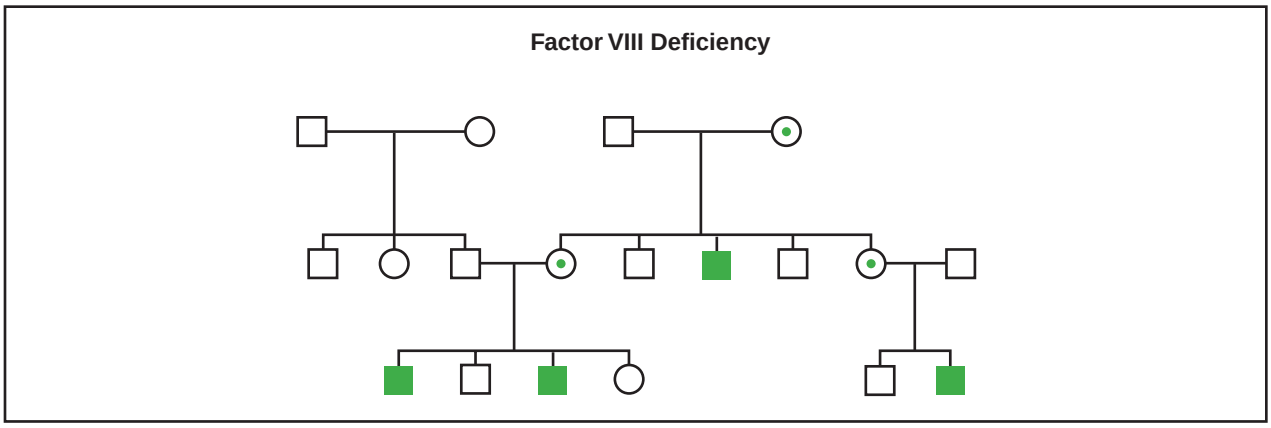
Elbow x ray showing changes to bone structure as a result of hemophilia. *(Custom Medical Stock Photo, Inc.)*

The following concepts are important to understanding the **inheritance** of these diseases. All humans have two **chromosomes** determining their gender: females have XX, males have XY. Because the trait is carried only on the X chromosome, it is called "sex-linked." The chromosome's flawed unit is referred to as the **gene**.

Both factors VIII and IX are produced by a genetic defect of the X chromosome, so hemophilia A and B are both sex-linked diseases. Because a female child always receives two X chromosomes, she nearly always will receive at least one normal X chromosome. Therefore, even if she receives one flawed X chromosome, she will still be capable of producing a sufficient quantity of factors VIII and IX to avoid the symptoms of hemophilia. Such a person who has one flawed chromosome, but does not actually suffer from the disease, is called a carrier. She carries the flaw that causes hemophilia and can pass it on to her offspring. If, however, she has a son who receives her flawed X chromosome, he will be unable to produce the right quantity of factors VIII or IX, and he will suffer some degree of hemophilia. (Males inherit one X and one Y chromosome, and therefore have only one X chromosome.)

In rare cases, a hemophiliac father and a carrier mother can pass on the right combination of parental chromosomes to result in a hemophiliac female child. This situation, however, is rare. The vast majority of people with either hemophilia A or B are male.

About 30% of all people with hemophilia A or B are the first member of their family to ever have the disease. These individuals have had the unfortunate occurrence of a spontaneous mutation; meaning that in their early development, some random genetic accident befell their X chromosome, resulting in the defect causing hemo-



(Gale Group)

philia A or B. Once such a spontaneous genetic mutation takes place, offspring of the affected person can inherit the newly-created, flawed chromosome.

Demographics

Hemophilia A affects between one in 5,000 to one in 10,000 males in most populations.

One recent study estimated the prevalence of hemophilia was 13.4 cases per 100,000 U.S. males (10.5 hemophilia A and 2.9 hemophilia B). By race/ethnicity, the prevalence was 13.2 cases/100,000 among white, 11.0 among African-American, and 11.5 among Hispanic males.

Signs and symptoms

In the case of severe hemophilia, the first bleeding event usually occurs prior to eighteen months of age. In some babies, hemophilia is suspected immediately, when a routine circumcision (removal of the foreskin of the penis) results in unusually heavy bleeding. Toddlers are at particular risk, because they fall frequently, and may bleed into the soft tissue of their arms and legs. These small bleeds result in bruising and noticeable lumps, but don't usually need treatment. As a child becomes more active, bleeding may occur into the muscles; a much more painful and debilitating problem. These muscle bleeds result in pain and pressure on the nerves in the area of the bleed. Damage to nerves can cause numbness and decreased ability to use the injured limb.

Some of the most problematic and frequent bleeds occur into the joints, particularly into the knees and elbows. Repeated bleeding into joints can result in scarring within the joints and permanent deformities. Individuals may develop arthritis in joints that have suffered continued irritation from the presence of blood. Mouth injuries can result in compression of the airway, and, therefore, can be life-threatening. A blow to the head, which might be totally insignificant in a normal individual, can result in bleeding into the skull and brain. Because the skull has no room for expansion, the hemophiliac individual is at risk for brain damage due to blood taking up space and exerting pressure on the delicate brain tissue.

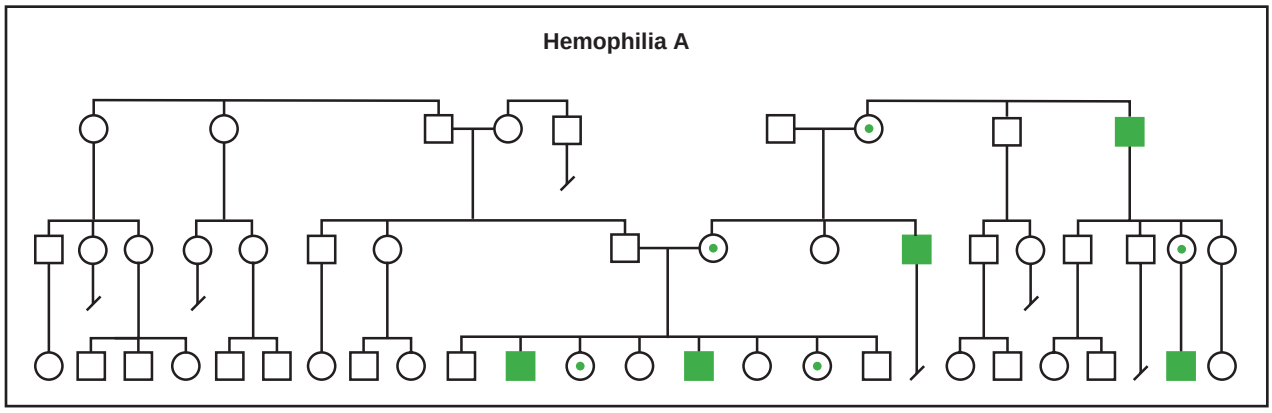
People with hemophilia are at very high risk of hemorrhage (severe, heavy, uncontrollable bleeding) from injuries such as motor vehicle accidents and also from surgery.

Some other rare clotting disorders such as **Von Willebrand disease** present similar symptoms but are not usually called hemophilia.

Diagnosis

Various tests are available to measure, under very carefully controlled conditions, the length of time it takes to produce certain components of the final fibrin clot. Tests called assays can also determine the percentage of factors VIII and IX present compared to normal percentages. This information can help in demonstrating the type of hemophilia present, as well as the severity.

Individuals with a family history of hemophilia may benefit from **genetic counseling** before deciding to have a baby. Families with a positive history of hemophilia can also have tests done during a pregnancy to determine whether the fetus is a hemophiliac. The test called chorionic villus sampling examines proteins for the defects that lead to hemophilia. This test, which is associated with a 1% risk of miscarriage, can be performed at 10–12 weeks. The test called **amniocentesis** examines the **DNA** of fetal cells shed into the amniotic fluid for genetic mutations. Amniocentesis, which is associated with a one in 200 risk of miscarriage, is performed at 16–18 weeks gestation.



(Gale Group)

Treatment and management

The most important thing that individuals with hemophilia can do to prevent complications of his disease is to avoid injury. Those individuals who require dental work or any surgery may need to be pre-treated with an infusion of factor VIII to avoid hemorrhage. Also, hemophiliacs should be vaccinated against hepatitis. Medications or drugs that promote bleeding, such as aspirin, should be avoided.

Various types of factors VIII and IX are available to replace a patient's missing factors. These are administered intravenously (directly into the patient's veins by needle). These factor preparations may be obtained from a single donor, by pooling the donations of as many as thousands of donors, or by laboratory creation through highly advanced genetic techniques.

The frequency of treatment with factors depends on the severity of the individual patient's disease. Patients with relatively mild disease will only require treatment in the event of injury, or to prepare for scheduled surgical or dental procedures. Patients with more severe disease will require regular treatment to avoid spontaneous bleeding.

While appropriate treatment of hemophilia can both decrease suffering and be life-saving, complications associated with treatment can also be quite serious. About 20% of all patients with hemophilia A begin to produce chemicals in their bodies which rapidly destroy infused factor VIII. The presence of such a chemical may greatly hamper efforts to prevent or stop a major hemorrhage.

Individuals who receive factor prepared from pooled donor blood are at risk for serious infections that may be passed through blood. Hepatitis, a severe and potentially fatal viral liver infection, may be contracted from pooled factor preparations. Recently, a good deal of concern has been raised about the possibility of hemophiliacs contracting a fatal slow virus infection of the brain (Creutzfeldt-Jakob disease) from blood products. Unfortunately, pooled factor preparations in the early 1980s were contaminated with human immunodeficiency virus (HIV), the virus which causes AIDS. A large number of hemophiliacs were infected with HIV and some statistics show that HIV is still the leading cause of death among hemophiliacs. Currently, careful methods of donor testing, as well as methods of inactivating viruses present in donated blood, have greatly lowered this risk.

The most exciting new treatments currently being researched involve efforts to transfer new genes to hemophiliacs. These new genes would have the ability to produce the missing factors. As yet, these techniques are not being performed on humans, but there is great hope that eventually this type of **gene therapy** will be available.

Prognosis

Prognosis is very difficult to generalize. Because there are so many variations in the severity of hemophilia, and because much of what befalls a hemophiliac patient will depend on issues such as physical activity level and accidental injuries, statistics on prognosis are not generally available.

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National Hemophilia Foundation. 116 West 32nd St., 11th Floor, New York, NY 10001. (800) 42-HANDI. <http://www.info@hemophilia.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Jennifer F. Wilson, MS

Hepatocellular carcinoma *see* **Liver cancer**

Hepatorenal glycogenosis *see* **Fanconi-Bickel syndrome**

Hereditary angioneurotic edema

Definition

Hereditary angioneurotic edema (HANE) is a non-sex-linked (autosomal) dominant disease that results from mutations in a **gene** responsible for producing one of the proteins responsible for human immunity. This disease is also known as hereditary angioedema (HAE) or hereditary C1 inhibitor deficiency because it is a deficiency of the protein (C1-INH) that inhibits the action of the enzyme known as C1 which causes this disease.

Description

There are two recognized forms of HANE. Type I represents approximately 80-85% of the cases of hereditary angioneurotic edema. In this type, the protein C1-INH is not produced in sufficient quantities. Type II HANE represents the remaining 15-20% of cases. In this type, C1-INH concentrations are normal, but the C1-INH protein produced is defective.

Related to the two types of hereditary angioneurotic edema are acquired types of this disease (AANE or AAE) that are not based on a defective gene. Type I AAE is caused by a disorder that causes over-growth (proliferation) of the lymph tissues and destroys C1-INH. Type II AAE is caused by the presence of autoantibodies (antibodies that attack the host organism that produced them) that destroy C1-INH. Both of these acquired forms of angioedema can generally be differentiated from the two types of HANE by the age of onset. Symptoms of the acquired diseases usually do not occur until the fourth decade of life, while those of the hereditary forms are generally present prior to puberty.

The human body has two distinct immune systems: the humoral immune system and the cell-mediated immune system. The complement system is a part of the humoral immune system. Humoral means within the humor, or fluids, of the body. Blood, lymph, and bile compose the fluids of the humor. The complement system uses at least 30 different proteins to "mark" any foreign cells in the body that do not have certain protective proteins on their cell membranes which identify them as belonging in the body. These complement proteins are designated C1, C2, C3, et cetera. Once the foreign cells have been "marked," a particular form of white blood cell, called a phagocyte, is dispatched to the area with the marked cells and destroys them.

Phagocytes will eventually destroy any cell that is marked by complement; therefore, it is important to make sure that the complement proteins are not marking non-foreign cells. When cells are improperly marked, these cells will also be destroyed, causing what is called an autoimmune response. In effect, this autoimmune response means that the body is recognizing itself as foreign and attempting to destroy healthy cells. Inhibitors of the various complement proteins are necessary to prevent these proteins from marking the wrong cells or from continuing to mark cells after the foreign cells have been destroyed.

C1 inhibitor (C1-INH) is a chemical that is involved in the regulation of the complement system by inhibiting the action of the first complement protein (C1). C1-INH acts by binding free C1 molecules in the humor, preventing them from being able to function. It also limits the activation of other complement proteins.

Because C1-INH is diminished or defective in people affected with HANE, C1 is not inhibited and this inappropriately initiates the complement reaction which causes the swelling (acute inflammatory response) characteristic of HANE.

C1-INH also binds to the chemicals kallikrein and plasmin that are involved in blood clotting. Kallikrein is

KEY TERMS

Acquired angioneurotic edema—Abbreviated AANE, or AAE, this is a non-hereditary form of angioedema that generally begins to show symptoms in, or after, the fourth decade of life.

Androgens—A group of steroid hormones that stimulate the development of male sex organs and male secondary sexual characteristics.

Angioneurotic edema—Recurrent episodes of swelling of the tissues of the body caused by an over-active immune system. This is also called angioedema.

C1 inhibitor—Abbreviated C1-INH, this protein is responsible for preventing the action of the C1 complement molecules in the body. It is this protein that is either deficient or malformed in HANE.

Complement system—Class III MHC (major histocompatobility complex) proteins capable of destroying invading organisms directly via natural immunity, as well as indirectly through an interaction with other components of the immune system.

Hereditary angioneurotic edema—Abbreviated HANE, or HAE, this is an inherited kind of angioneurotic edema. Type I HANE is caused by a deficiency of C1-INH. Type II HANE is caused by a malformation of the C1-INH protein.

Kallikrein—A protein necessary for the activation of chemicals that cause dilation of blood vessels to allow increased blood flow to an area that requires more blood than normal. It is also capable of cleaving the complement, C5, into C5a, a much more robust and active form of this complement molecule.

Phagocyte—White blood cells capable of engulfing and destroying foreign antigen or organisms in the fluids of the body.

Plasmin—The blood protein that is responsible for dissolving blood clots.

Urticaria—Also known as hives. Usually associated with an allergic reaction.

necessary for the activation of chemicals that cause dilation of blood vessels to allow increased blood flow to an area that requires more blood than normal. Plasmin is the chemical responsible for dissolving blood clots. A lack of binding of plasmin means that the formation of initial blood clots is difficult, a problem that is exacerbated by high levels of unbound kallikrein, which allows higher than normal blood flow.

With the absence or dysfunction of the C1-INH protein, the functions of blood flow, blood clotting, and immune response are impaired in individuals affected by hereditary angioneurotic edema, leading to swelling of the bodily tissues.

Genetic profile

The central Pyncheon family in Nathaniel Hawthorne's *The House of the Seven Gables* carries an ancestral curse of dying from choking on their own blood. Hawthorne describes members of the family who made odd sounds in the throat and chest when agitated, and sometimes died from choking: "This mode of death has been an idiosyncrasy with his family, for generations past....[the] prophecy was probably founded on a knowledge of this physical predisposition in the Pyncheon race." It seems possible that Hawthorne was not only describing the symptoms of HANE but also acknowledging it to be an inherited genetic disorder.

All hereditary forms of HANE are caused by mutations in the gene responsible for the production of C1-INH. This gene is located on the long arm (q) of chromosome 11, at the specific location q11.2-q13. There are at least 13 different mutations of the C1-INH gene that cause the symptoms of HANE. Six of these are known to cause type I HANE, while another six are known to cause type II HANE. The final mutation has only been found in one individual. In this case, an acquired form of angioedema was determined to be caused by a mutation in a different region of the C1-INH gene than those mutations causing type I or type II cases of HANE.

Demographics

HANE affects approximately 50,000 people in the United States and Europe. It is estimated to occur in approximately one in every 50,000 to 150,000 live births. HANE appears to affect males and females equally and does not have a racial preference.

As an autosomal dominant trait, only one copy of an abnormal gene needs to be inherited for an individual to be affected. Therefore, if one child is affected with HANE, the likelihood that a second child will be affected with HANE is 50%. In cases of parents related by blood (consanguineous parents) the likelihood of HANE is increased.

Signs and symptoms

Individuals affected with either form of HANE have episodes of swelling of the hands, feet, trunk, face, digestive tract, and airways (angioneurotic edema or angioedema). These attacks of angioedema are often accompanied by attacks of nausea, vomiting, and abdominal pain. The frequency and severity of these attacks is not predictable and varies from individual to individual. These attacks may occur without cause, or they may be triggered by anxiety, stress, or minor traumas, such as dental procedures. If these symptoms are accompanied by hives (urticaria) a diagnosis other than HANE is indicated.

Symptoms of HANE generally first occur prior to puberty and episodes generally increase in severity after puberty.

Diagnosis

A diagnosis of HANE is suspected in individuals who have recurrent attacks of swollen tissues (angioedema). Diagnosis of type I HANE is confirmed by blood tests showing abnormally low levels of C1-INH, C2, and C4. Diagnosis of type II HANE is confirmed by blood tests showing normal levels of C1-INH and C2, but abnormally low levels of C4. Abnormally low levels of C1-INH and C4 without the presence of autoantibodies suggest a diagnosis of type I acquired angioedema, while abnormally low levels of C1-INH and C4 and the presence of autoantibodies suggest a diagnosis of type II acquired angioedema.

Hives (urticaria) are not generally associated with HANE. If hives are present with tissue swelling, this may suggest an allergic reaction, not a case of HANE. Occasionally, individuals affected with HANE also develop hives, but they are usually secondary to the angioedema. In a severe allergic reaction, hives are generally prominent as the major symptom.

Treatment and management

The treatment of both hereditary forms of angioedema is the same. Androgens (male sex hormones) such as winstrol, danazol, and oxandrolone have been shown to be effective in preventing chronic recurrences of swelling. These drugs are seldom used to treat acute attacks. In instances of abdominal attacks, fluid replacement therapy via intravenous injection may be required. Demerol and Compazine suppositories are often prescribed to relieve abdominal pain and vomiting.

Edema (swelling) of the airways is the most life-threatening feature of HANE. Without prompt medical attention, individuals affected with HANE can die from an obstruction of the airway caused by this swelling. Unfortunately, if the attending physician does not recognize HANE, attempts at tracheal intubation (formation of an airway directly in the neck) may aggravate the swelling rather than produce a functioning airway.

Treatment with vapor-heated C1-INH concentrate has proven to be an effective treatment both as a prophylactic (preventative) and a treatment for acute attacks of angioedema in all individuals affected with HANE. The C1-INH concentrate is derived from human blood plasma; therefore it may possibly be contaminated. It is vapor-heated to inactivate possible hepatitis and HIV viruses. However, because HANE is a disease of the immune system, many doctors are reluctant to use C1-INH from other people and many patients are unwilling to accept such a treatment. The use of human recombinant C1-INH should alleviate any concerns arising from possible contamination of the blood supply.

Androgens are still the preventative treatment of choice because they are more cost-effective than treatments with C1-INH. However, androgens should not be given to women who are pregnant, or who might become pregnant. In these cases, C1-INH treatment is required.

In 1999, the U.S. Food and Drug Administration granted Orphan Drug Designations to human recombinant C1-INH for both preventative and acute treatment of HANE. On March 21, 2000, Baxter Healthcare's Hyland Immuno division and Europe's Pharming Group announced an agreement to jointly develop recombinant human C1-INH. As of the March 2000 press release by these two companies, pre-clinical (animal) studies were expected to be completed in late 2000 and phase I human trials were slated to begin in late 2000 or early 2001. Because of the Orphan Drug Designations from the USFDA, this possible treatment for HANE is automatically "fast-tracked," which means that it could potentially be approved for human use by 2004.

Prognosis

The key to successful management of HANE is a proper medical diagnosis. With proper medical treatment, HANE is completely controllable and individuals affected with HANE suffer no diminishment in quality of life.

Resources

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ORGANIZATIONS

Hereditary Angioedema Association. PO Box 492, Live Oak, FL 32064. <http://www.hereditaryangioedema.com>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paul A. Johnson

Hereditary arthro-opthalmopathy *see* **Stickler syndrome**

Hereditary colorectal cancer

Definition

Hereditary colorectal cancer is cancer of the colon or rectum that develops chiefly as the result of inherited factors.

Description

The colon, or the large intestine, is a long muscular tube that absorbs water from stool and advances the stool towards the rectum. The rectum works in conjunction with the anus to coordinate the process of defecation. The colon and rectum are jointly referred to as the colorectum.

A neoplasm is a portion of abnormal tissue that grows rapidly and out of control. Cancer is the malignant type of neoplasm. Colorectal cancer is a relatively common and dangerous cancer. Tumors originate in the mucosa, or inner lining of the colorectum, and grow inwardly. Eventually, the tumor spreads outwardly until it reaches lymph nodes or other organs in the abdomen. Ultimately, cancer cells may detach from the original tumor and spread to distant parts of the body (such as the liver, lungs, bone, and brain) in a process called metastasis.

The development of colorectal cancer is not a random event, but rather arises in a sequential fashion. The first easily detected step is the appearance of adenomatous polyps. Polyps are grossly defined as elevations of a surface. An adenomatous polyp is derived from the glandular elements of the mucosa. A person may have any number of colorectal adenomatous polyps. Eventually, one or more of these polyps may transform into a cancer. The risk of colorectal cancer increases with the number of polyps. Larger polyps are also more likely to become cancerous than smaller ones. The factors that initiate this adenoma-cancer sequence are inherited and/or acquired from the environment.

Colorectal cancer occurs in certain families much more often than expected by chance alone. In fact, an important and common risk factor for the development of colorectal cancer is the occurrence of colorectal cancer in the family. About 10% of people have a first-degree relative with colorectal cancer. Having a first-degree relative with colorectal cancer increases the chance of developing colorectal cancer by two- to three-fold. The risk becomes even higher when colorectal cancer occurs in a relative at an early age (before 50 years of age) or when more than one relative has the cancer. This suggests that susceptibility of developing colorectal cancer in affected families is due to inherited factors, although shared exposure to environmental stimuli may play a role. Scientists are investigating the genetic factors that may be responsible for the increased risk of colorectal cancer in these cases of common **inheritance**.

The vast majority of cases of colorectal cancer are sporadic; that is, they occur in the absence of a hereditary syndrome, although familial risk may be involved. But rarely, colorectal cancer is inherited as part of a well-defined syndrome. These syndromes altogether account for about 2-5% of all cases of colorectal cancer.

Familial adenomatous polypyposis

In the syndrome of **familial adenomatous polyposis** (FAP), adenomas develop in the colon and rectum

early in life, at an average age of 15 years. Eventually, hundreds to thousands of adenomas will develop. The presence of such a large number of adenomas ensures that at least one of these adenomas will develop into cancer if the colon is not surgically removed. In people with FAP, the average age of occurrence of colorectal cancer is 39. Some patients will develop cancer in their teens and almost every patient will have cancer by age 45.

Other types of polyps are also common in patients with FAP. Polyps may develop in the stomach or duodenum. Those in the stomach are benign, while those in the duodenum may become malignant. The cancer risk in these other polyps is much less than the risk associated with the colorectal polyps. Patients with FAP may also have abnormalities outside the gastrointestinal tract, such as osteomas, desmoid tumors, extra teeth, and hypertrophy of the retinal pigment epithelium.

Three variants of FAP have been identified. Gardner syndrome is a rare variant of FAP characterized by colorectal polyps and a marked prominence of extraintestinal growths. Examples of the growths include osteomas, epidermoid cysts, and desmoid tumors. Although these growths usually present only cosmetic problems, desmoid tumors can occasionally compress nearby tissue in a harmful way.

Turcot syndrome is another rare type of FAP. Patients with this syndrome have the typical colorectal polyps, as well as malignant tumors of the central nervous system such as medulloblastoma, astrocytoma, ependymoma, and glioblastoma multiforme.

Patients with the attenuated adenomatous polyposis coli form of FAP have many colonic polyps, but not the hundreds or thousands seen in typical FAP. The chance of developing colon cancer approaches but does not reach 100%, and colon cancer usually appears later than in patients with typical FAP.

Hereditary nonpolyposis colorectal cancer

Patients with hereditary nonpolyposis colorectal cancer (HNPCC) have about an 80% risk of developing colorectal cancer if untreated. They may have more polyps than the general population, but not the hundreds or thousands of polyps associated with FAP. The average age for the development of cancer is 45 years old. Frequently, a patient with HNPCC will have multiple cancers at the same time (synchronous) or may develop cancers at different time periods (metachronous).

Extraintestinal cancers sometimes occur in HNPCC. The most common is uterine cancer, but other examples include cancer of the uterus, stomach, small intestine, pancreas, kidney, and ovary.

The Amsterdam criteria are clinical criteria for the diagnosis of HNPCC in a family:

- At least three relatives with colorectal cancer, one of whom must be a first-degree relative of the other two.
- Colorectal cancer involving at least two generations.
- One or more cases of colorectal cancer before the age of 50.

Muir-Torre syndrome is a rare form of HNPCC. In addition to polyps and cancer of the colon and rectum, patients exhibit various types of skin cancer.

Genetic profile

It must be understood that all colorectal cancers stem from genetic mutations. Environmental factors may also contribute to the development of cancer. Sometimes colorectal cancer appears in a patient who has neither affected relatives nor an inherited syndrome. Other cases appear in families that seem genetically susceptible to the development of these cancers. The presence of colorectal cancer in relatives, especially young relatives, increases the risk of developing colorectal cancer. In families affected by the rare syndromes of hereditary colorectal cancer (HNPCC, FAP, and their variants), the genetic mutations are inherited in autosomal dominant fashion.

Whether it appears sporadically or is inherited as part of a syndrome, colorectal cancer is generally linked to mutations in certain categories of genes: proto-oncogenes, tumor suppressor genes, **DNA** mismatch repair genes, or modifier genes. The proto-oncogene category inludes the *K-ras*, *src*, and *c-myc* genes. The tumor suppressor genes are the APC (adenomatous polyposis coli) gene, the DCC (deleted in colon cancer) gene, the MCC (mutated in colon cancer) gene, the DPC4 gene, and p53. The mismatch repair genes are hMLH1, hMSH2, hPMS1, hPMS2, and hMSH6/GTBP. The modifier genes inlude the COX2 (cyclooxygenase 2) gene, the CD44v gene, and the phospholipase A2 gene.

The genetic defect in FAP and its three variants (Gardner syndrome, Turcot syndrome, and attenuated adenomatous polyposis coli) reside on the APC gene, which is on the long arm of chromosome 5. However, there are a wide variety of mutations within the APC gene that can result in those syndromes. Sometimes Turcot's syndrome is associated with the same mutations as those in HNPCC. Mutations of mismatch repair genes, such as hMLH1, hMSH2, hPMS1, hPMS2, and hMSH6/GTBP, are characteristic of the HNPCC syndrome. The transmission of these hereditary colorectal cancer syndromes occurs through mutations of the same genes that are mutated in sporadic cases of colorectal cancer. But it must be emphasized that the hereditary colorectal cancer

KEY TERMS

Adenomatous—Derived from glandular structures.

Astrocytoma—Tumor of the central nervous system derived from astrocytes.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Central nervous system—In humans, the central nervous system is composed of the brain, the cranial nerves and the spinal cord. It is responsible for the coordination and control of all body activities.

Computed tomography—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Desmoid tumor—Benign, firm mass of scarlike connective tissue.

Distal—Away from the point of origin.

Endoscopy—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

Ependymoma—Tumor of the central nervous system derived from cells that line the central canal of the spinal cord and the ventricles of the brain.

Epidermoid cyst—Benign, cystic tumor derived from epithelial cells.

Glioblastoma multiforme—Tumor of the central nervous system consisting of undifferentiated glial cells.

Medulloblastoma—Tumor of the central nervous system derived from undifferentiated cells of the primitive medullary tube.

Metachronous—Occurring at separate time intervals.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Osteoma—A benign bone tumor.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Prophylactic—Preventing disease.

Proximal—Near the point of origin.

Synchronous—Occurring simultaneously.

syndromes are inherited in an autosomal dominant pattern. This means that each child of an affected person has a 50% chance of inheriting the disease.

Families with the inherited syndromes of colorectal cancer can undergo **genetic testing** to determine which individuals have inherited the disease. The tests for the defective genes can detect the mutation in approximately 60 to 80% of FAP families and about 50% of HNPCC families. However, if one person is found to have the mutation, the other family members can be tested with nearly 100% accuracy. Although genetic testing can provide useful information to the patients, it may be associated with psychosocial risks. Thus, genetic testing should be performed only in formal programs. **Genetic counseling** should also be provided.

Demographics

Colorectal cancer is relatively common with approximately 160,000 new cases diagnosed each year, but the syndromes of inherited colorectal cancer are rare. It is estimated that they comprise only 2-5% of all cases of colorectal cancer. FAP occurs in about one in every 10,000 births. The incidence of all colorectal cancer increases with age.

Signs and symptoms

The clinical manifestations of colorectal cancer depend largely on location and tumor size. Tumors in the proximal colon can grow to large sizes before detection. They may cause weight loss, abdominal pain, or bleeding. The bleeding may be readily noticed by the patient as frank blood in the toilet, or smears of blood in the stool. Less extensive bleeding may be detected by the fecal occult blood test, in which a sample of stool obtained during a rectal exam is tested for microscopic amounts of blood. Anemia, or low red blood cell count, detected by a laboratory test may prompt further examination of the colon to determine if a tumor is the source of bleeding. In the smaller, distal colon, tumors are more likely to cause obstruction. This may cause gas pains and decrease in the caliber of the stool. Additionally, these cancers may cause bleeding or a change in bowel habits. In FAP, the first symptom is usually diarrhea.

Diagnosis

The presence of symptoms such as abdominal pain, weight loss, change in bowel habits, or decrease in stool caliber may point to a diagnosis of colorectal cancer. Of course, these symptoms must be interpreted within the context of the patient's age, previous medical history, and family history of colorectal cancer.

Ideally, the diagnosis of colorectal cancer should be made before symptoms develop. A number of screening tests are useful for detecting colorectal cancer. The fecal occult blood test that was discussed earlier is a simple test performed in the office. The normal result is the absence of blood in the stool. If blood is found in the stool, the suspicion for colorectal cancer becomes higher. Standard screening also includes an endoscopic exam—either sigmoidoscopy or colonoscopy. In these exams, a thin, specially lighted tube is inserted directly into the anus and advanced into the colon. The physician can view the inside of the colon and check for polyps or tumors. Sigmoidoscopy allows examination of the lower part of the colon while colonoscopy allows a more extensive view. Sometimes a barium enema is added to the screening procedure. In this test, a dye is injected into the anus and up into the colon. The dye coats the inside of the colon so that tumors can be detected by plain x ray.

New screening tests are currently under investigation. In wireless endoscopy, a tiny pill-sized camera is swallowed. As the camera traverses the gastrointestinal tract, it transmits video footage that can be examined for suspicious abnormalities. Eventually the camera is passed out of the anus with the stool. Virtual colonoscopy generates a three-dimensional image of the colon by applying advanced computer graphics technology to images obtained by computed tomography (CT) scanning. These processes can spare the patient the usual discomfort of traditional endoscopy. However, they are not yet fully developed nor approved for colorectal cancer screening.

If any of the above screening tests identifies an abnormality that appears to be a tumor, the diagnosis must be confirmed by biopsy. This is performed during colonoscopy. A small piece of tissue is removed and examined in the laboratory for cancerous cells.

Most medical organizations recommend that screening should begin in the general population at age 40 to 50. The fecal occult blood test is performed annually and sigmoidoscopy every three to five years. If a first degree relative has colorectal cancer, then screening should begin at 35 to 40 years of age. Alternatively, screening can begin five years earlier than the age of a young relative who has colorectal cancer.

Individuals in families affected by hereditary colorectal cancer syndromes are at high risk for developing cancer early in life. Therefore, screening is initiated at a young age. Screening can be reserved for those family members who have been proven to carry the abnormal gene by genetic testing, or it can be applied to all family members if the specific mutation cannot be identified. Some experts propose that in families with a history of FAP, screening should begin at 10 to 12 years of age and be repeated every one to two years. In families with HNPCC, colorectal screening should begin at 20 to 30 years of age and also be repeated every one to two years.

Since FAP and HNPCC are also associated with other cancers, affected patients should undergo appropriate screening for these malignancies as well. Those with FAP require regular upper endoscopy to detect tumors of the stomach and duodenum. Women with HNPCC should undergo screening for uterine cancer by way of random biopsies of the inner lining of the uterus.

Treatment and management

The treatment of sporadic colorectal cancer requires surgical removal of the tumor and surrounding tissue. Chemotherapy or radiation therapy may also be necessary. But the treatment of colorectal cancer in the hereditary syndromes is more aggressive. In these cases, the entire colon must be removed, since cancer will almost certainly develop in any remaining colon. Sometimes the rectum is also removed; alternatively, the patient may undergo frequent examination of the rectum for polyps or cancers. Experts strongly recommend that individuals with known FAP should consider surgical removal of the colon and/or rectum early in life as a prophylactic measure, before cancer is diagnosed. Although the role of prophylactic surgery in patients with HNPCC is less well-defined, many experts favor it. The patient faces a choice between prophylactic surgery and frequent, lifelong screening.

Some studies have shown that the drug sulindac may reduce the number of adenomatous polyps that develop in FAP and its variants. In addition, certain nonsteroidal antiflammatory drugs such as aspirin may also reduce the incidence of colorectal cancer in general.

Prognosis

Patients with a hereditary colorectal cancer syndrome such as FAP, HNPCC, or its variants, have a much higher likelihood of developing colon cancer than the general population. In the extreme case of typical FAP, essentially 100% of patients will develop colon cancer without surgery. If colon cancer does develop, survival depends on the extent to which the cancer has spread. Cancer that is isolated to the colon is associated with much better survival than cancer that has spread to distant organs such as the liver or lungs.

Resources

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Kevin Osbert Hwang, MD

Hereditary desmoid disease

Definition

Hereditary desmoid disease (HDD) is a condition that causes people to develop a benign (noncancerous) growth known as a desmoid tumor. Desmoid tumors may also be called fibromatosis.

Description

In HDD, multiple family members from several generations develop desmoid tumors. These tumors are very rare. They account for fewer than 0.1% of all tumors diagnosed. The term "desmoid" comes from the Greek word for "band." That describes these tumors well, as they have a tendon- or ligament-like appearance. They usually occur in the abdomen, but they may also develop in the neck, chest, arms, and legs.

Desmoid tumors may appear due to mutations, or changes, in a **gene** called adenomatous polyposis coli (APC). Most desmoid tumors, though—more than 97%—occur sporadically, meaning that they are not caused by genetic mutations. People who develop sporadic desmoid tumors have no other health problems associated with mutations in the APC gene and have no close family members with the tumors. In the past desmoid tumors were classified as fibrosarcomas (growths associated with **cancer**), but this is no longer the case.

Mutations in the APC gene usually result in **familial adenomatous polyposis** (FAP). This condition causes hundreds to thousands of polyps (tiny growths) to develop in the colon. It is associated with a high risk for developing colon cancer. People who have FAP need to have their health monitored on a regular basis. Colon cancer can be prevented by careful medical screening and removal of the colon.

Some families with FAP develop extra-colonic symptoms (involving organs other than the colon), including desmoid tumors. The combination of colon polyposis and desmoid tumor was once termed "Gardner's syndrome," but it is now known that the two conditions are the same. Other extra-colonic features seen in families with FAP are cysts in the jawbone, skin cysts (epidermal cysts), bony bumps on the skull, a specific kind of spot on the retina, and thyroid cancer. About 10% of people with FAP will develop desmoid tumors. However, the risk differs from family to family.

In HDD, multiple family members over two or more generations develop desmoid tumors, but not colon polyposis. Family members in subsequent generations will have an increased risk of developing desmoid tumors.

Genetic profile

Every person diagnosed with HDD has a 50% chance of passing on the condition to each of his/her children. The chances that a child who has the **gene mutation** associated with HDD will develop a desmoid tumor are thought to be very high, maybe even 100%. It is possible that there may be other genes involved in HDD, but no gene other than APC has been identified. The location of the mutation within the APC gene may predict the symptoms and health problems that a person will experience, but this association is far from perfect.

Demographics

Hereditary desmoid disease is a rare condition. As of 2001, only four families have been reported in the medical literature. (It is likely, however, that not all families with HDD have been described in the literature.) Males and females are equally affected.

Signs and symptoms

Desmoid tumors may cause a noticeable lump and/or pain.

Diagnosis

HDD is usually diagnosed solely upon family history. Evaluation for HDD requires filling out a detailed, three-generation family tree. Medical records and/or death certificates should also be examined to confirm or clarify possible diagnoses of desmoid tumors. Medical records for family members developing colon polyps and/or undergoing colon surgery will also be requested in order to evaluate for FAP.

Genetic (or diagnostic) testing for APC gene mutations (changes) is another way of making a diagnosis. It may be offered to someone who has developed a desmoid tumor and has a family history of such tumors. If a mutation is identified, the positive test result provides proof of the diagnosis. If no mutation is identified, this negative

test result does not necessary remove the diagnosis of HDD.

Diagnostic testing for HDD may be offered to an individual who has no personal history of a desmoid tumor but whose family history is strongly suggestive of HDD. Prenatal diagnosis of HDD is available only if an APC genetic alteration has already been identified in the family. Such "predictive" **genetic testing** is best done with a geneticist (a doctor specializing in genetics) and/or a genetic counselor.

Treatment and management

There is no cure for HDD, nor a method for preventing it. Treatment depends upon the location of the tumor and may include one or more of the following: surgery, chemotherapy, hormonal therapy, and/or radiation. In addition, everyone diagnosed with a desmoid tumor should be evaluated for FAP. This evaluation will include a detailed family history as well as colon screening though sigmoidoscopy or colonoscopy.

Treatment is not required until a tumor develops. Someone who has symptoms, however, must have regular medical check-ups.

There are no proven methods of screening for or preventing desmoid tumors, but it is suggested that people with or at risk for HDD have physical examinations every year. It is very important that an individual's physician be aware of the family history and the risk of developing a tumor.

Prognosis

An individual who has a genetic mutation for HDD has a high chance of developing a desmoid tumor. However, the condition is treatable. Prognosis may be affected by a person's overall condition, so being healthy and engaging in healthy behaviors increase the chances of a good outcome.

Resources

ORGANIZATIONS

HCCA. 3601 N. 4th Ave. # 201, Sioux Falls, SD 57104. (800) 264-6783. <http://www.hereditarycc.org/index.html>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

Association of Cancer Online Resources. *The Desmoid Tumor Online Support Group*. <http://listserv.acor.org/archives/desmoid.html>.

KEY TERMS

Colonoscopy—Procedure for viewing the large intestine (colon) by inserting an illuminated tube into the rectum and guiding it up the large intestine.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Polyposis—A descriptive term indicating that hundreds to thousands of polyps have developed in an organ.

Sigmoidoscopy—The visual examination of the inside of the rectum and sigmoid colon, using a lighted, flexible tube connected to an eyepiece or video screen for viewing.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

OncoLink. <http://www.oncolink.upenn.edu/about_oncolink>.

The University of Texas, MD Anderson Cancer Center. <http://search.mdanderson.org/compass>.

Cindy L. Hunter, CGC

Hereditary hearing loss and deafness

Definition

Hereditary hearing loss and deafness refers to the genetically caused loss or partial impairment of the ability to hear. It is estimated that at least half of the people with hearing loss and/or deafness in the developed world have it as the result of genetic causes.

Description

Genetic forms of hearing loss can be congenital (present from birth) or delayed onset. These hearing losses can be progressive, in which the hearing impairment increases with time; or non-progressive, in which the hearing loss is stable over time. Both ears (bilateral) or only one ear (unilateral) may be affected and the hearing loss may be equal in both ears (symmetric) or different in

each ear (asymmetric). Hearing loss may be the only finding the affected person has (non-syndromic hereditary hearing loss) or the hearing loss may be associated with other findings associated with a specific genetic syndrome (syndromic hereditary hearing loss). Hereditary hearing losses cover the entire range from mild hearing loss to total deafness. Additionally, the hearing loss can be of the conductive, sensorineural, or mixed type.

Conductive hearing loss results from a blockage of the auditory canal or some other dysfunction of the eardrum or one of the three small bones within the ear (the stapes, the malleus, and the incus) that are responsible for collecting sound. In hearing, sound vibrations enter the large fleshy part of the ear that is external to the head (the pinna) and travel down the auditory canal striking the eardrum (tympanic membrane), which begins to vibrate. As this membrane vibrates it touches the first of a series of three small bones (the malleus, the incus, and the stapes) that mechanically transfer the vibrations to the cochlea. The cochlea is a fluid-filled tube that bends back on itself such that the two open ends lie one on top of the other. One end is covered by a membrane called the oval window, while the other end is covered by a membrane called the round window. It is the oval window that is struck by the stapes. Since the cochlea is filled with fluid, the oval window cannot vibrate without the assistance of the round window: as the oval window is pushed in by the stapes, the round window bulges out; as the oval window oscillates out, the round window bulges inward.

The vibrations imparted to the oval window by the stapes striking the round window are picked up by the organ of Corti within the cochlea. It is this structure that is the true receptor, in a nerve sense, of sound waves. The organ of Corti consists of hair cells embedded in a gelatinous membrane (the tectorial membrane) that rest on a basilar membrane. Sensory neurons terminate on the hair cells of the organ of Corti. Vibration of the fluid in the cochlea causes the basilar membrane to move, which causes the hairs to bend creating an electrical signal. This is picked up by the sensory neurons and transferred to the auditory nerve (or cochlear nerve), which sends the impulse to the brain. Sensorineural hearing loss results from a dysfunction of the auditory nerve. In conductive hearing loss, the auditory nerve is normal.

Mixed type hearing loss involves both conductive and sensorineural types of hearing impairment.

The ear is also involved in maintaining balance. As a result, many individuals affected with hearing loss may also have balance problems. Body position, body movement, and balance are assisted by the vestibular apparatus of the inner ear, which consists of three functional parts. Two of these, the saccule and the utricle, signal what the body position is relative to gravity. The third structure of the vestibular apparatus is the semicircular canal, of which there are three in each ear. These canals contain structures (ampulae) that detect movement of the internal fluid of the canals as the head moves. Most hearing impaired people with balance problems experience difficulties with the proper functioning of the semicircular canals. Since the function of these canals is partially duplicated by the functioning of the saccule and the utricle, most individuals can "learn" to use these other systems to compensate for the dysfunction in the semicircular canals. Therefore, balance problems associated with hearing loss usually diminish over time.

Syndromic hearing loss

Syndromic hearing loss is generally classified by the overall syndrome that leads to hearing impairment. Based on a database search conducted in 1995 for the National Institute on Deafness, there are at least 396 multi-symptom genetic syndromes in which hearing loss is indicated as a major feature. As a part of this work, Dr. G. Bradley Schaefer compiled a list of the top ten syndromes in terms of incidence and prevalence in the population. This list, in order of prevalence, is: hemifacial microsomia and related oculo-auriculo-vertebrali (OAV) spectrum disorders; **Stickler syndrome**; congenital cytomegalovirus (not genetic); **Usher syndrome**; **branchiootorenal** (BOR) **syndrome**; **Pendred syndrome**; **CHARGE association**; neurofibramatosis 2; mitochondrial disorders; and **Waardenburg syndrome**. Other syndromes of which hereditary hearing loss is a feature include: the oto-palatal-digital syndromes; the **oral-facial-digital syndromes**, skeletal dysplasias (particularly **osteogenesis imperfecta**); metabolic storage disorders (particularly mucopolysaccharidoses and **Refsum disease**); Townes-Brock syndrome; and Wildervank syndrome. Each syndrome within each group may be quite rare, but the combined number of individuals affected with hereditary hearing loss in each group of syndromes is significant.

Non-syndromic hearing loss

Non-syndromic hearing loss is generally classified by the age of onset, the degree of audiological impairment, the progressive or non-progressive nature of the impairment, and the mode of **inheritance**.

Otosclerosis is the most common form of non-syndromic progressive conductive hearing loss in adults. It is caused by a growth of the spongy bone tissue in the middle ear which prevents the ossicles (malleus, incus, stapes) from being able to move as well as they once did. In certain advanced cases of otosclerosis, there may also be damage to the auditory nerve (sensorineural hearing

loss). Otosclerosis may be observed in teenagers, but it is generally first observed in people between the ages of 20 and 50. It is very rare for otosclerosis to occur past the age of 50.

Dominant progressive hearing loss (DPHL) and prebycusis (hearing loss related to aging) are the most common forms of non-syndromic progressive sensorineural hearing loss. DPHL tends to have an earlier age of onset than prebycusis, but this is highly variable between families. Within families, the age of onset of DPHL is generally fairly constant. The typical age of onset of DPHL is early childhood, but in some families it does not show symptoms until early or middle adulthood. Some individuals affected with DPHL also have problems with balance because of an alteration of the semicircular canal structures within their inner ears. These balance problems are not observed in other individuals with DPHL, suggesting that DPHL is caused by more than one **gene** or **gene mutation**. Prebycusis is not thought to be due to genetic causes. It is the most common form of hearing loss and everyone who lives beyond a certain age develops it to some degree. Prebycusis is thought to be caused by the combined effects of aging and the noises from the environment that a person has been exposed to. People who live, work, or entertain themselves in loud environments generally develop prebycusis to a greater degree than those people who exist in quieter surroundings.

Genetic profile

As of early 2001, mutations in at least 70 separate genes have been determined to cause hereditary hearing loss. This number is expected to increase markedly as the genetic mutations causing the nearly 400 syndromes associated with hearing loss are identified.

Approximately 75-80% of non-syndromic hereditary hearing loss is due to mutations that are autosomal (non-X linked) recessive. Approximately 20% are due to autosomal dominant gene mutations. The rare remaining cases of non-syndromic hereditary hearing loss are attributed to X-linked disorders. Mutations in the mitochondrial **DNA**, which are just beginning to be understood, may contribute to many cases of hereditary hearing loss that have formerly been assigned to one of the above categories by inheritance patterns alone, not on the basis of knowledge of the involvement of a specific gene.

While most genetic data is carried on the **chromosomes** in the nucleus of the cell, there are also tiny chromosomes in the mitochondria of cells. The method of inheritance of mitochondrial abnormalities is nearly exclusively maternal (through the mother). The mitochondria that develop in a human are almost all produced by replication of the maternal mitochondria from the egg, or ovum. The sperm contains almost no mitochondria. The percentage of hereditary hearing loss due to abnormalities in mitochondrial DNA is not yet known. Hearing loss due to mitochondrial inheritance may be either syndromic or non-syndromic. Mitochondrial mutations are known to be the cause of at least some of the adult onset hearing loss seen in individuals also affected with **diabetes mellitus**.

Otosclerosis is inherited via an autosomal dominant mutation located at the terminal end of the q arm of chromosome 15 (15q26.1-qter). The inheritance characteristics of otosclerosis show reduced penetration. A dominant condition with complete penetrance should show symptoms of the gene mutation in all individuals possessing the mutation (100% penetrance). However, because of the age-related symptoms of otosclerosis, many individuals possessing the genetic mutation known to cause otosclerosis do not have any symptoms of the disease. Similarly, when obtaining a family history, it is very possible that individuals from previous generations died of other causes prior to showing any signs of being affected with otosclerosis.

DPHL is transmitted between generations via one of several autosomal (non X-linked) dominant genes called the DFNA genes. By early 2001, 18 genes had been identified as DFNA genes. Children of a parent with DPHL have a 50% chance of inheriting the altered gene and having hearing loss. If both parents have DPHL each child has a 75% chance of inheriting hearing loss. DFNA1 has been localized to chromosome 5, while DFNA3 has been localized to chromosome 13.

Demographics

Deafness is estimated to affect 1.3 to 2.3 out of 1,000 children in the United States. Partial hearing loss is suspected to affect more than double that number. In adults, the incidence of some form of hearing loss is much higher than in children. As the population ages, the percentage of Americans affected with some type of hearing impairment is likely to climb.

It is estimated that approximately 10% of the population of the United States has partial hearing loss or deafness. This number is higher worldwide because non-genetic causes of hearing loss that are no longer as prevalent in the United States are still affecting individuals in many other parts of the world. These non-genetic causes of hearing impairment or loss include rubella, premature birth, meningitis, and incompatibility in the Rh blood factor between mother and fetus.

From studies of pupils at schools for the deaf in the United States, it is estimated that approximately 50% of

KEY TERMS

Audiogram—A graph of hearing level versus frequency. An audiologist plots the hearing loss of a patient on this graph to help determine the type of hearing loss and possible treatments.

Auditory nerve—The nerve responsible for transmitting electrical impulses created within the ear in response to sounds to the brain.

Conductive hearing loss—Hearing loss that is the result of a dysfunction of the parts of the ear responsible for collecting sound. In this type of hearing loss, the auditory nerve is generally not damaged.

Dominant progressive hearing loss—The main type of non-syndromic progressive sensorineural hearing loss seen in humans.

Hearing threshold—The minimum sound level at which a particular individual can hear. This is also called the hearing level (HL) of that person.

Mitochondria—Organelles within the cell responsible for energy production.

Mixed type hearing loss—Hearing loss that involves both conductive and sensorineural losses.

Non-syndromic hearing loss—Hearing loss that is not accompanied by other symptoms characteristic of a larger genetic syndrome.

Ossicles—Any of the three bones of the middle ear, including the malleus, incus, and stapes.

Otosclerosis—The main type of non-syndromic progressive conductive hearing loss seen in humans. In very advanced cases, otosclerosis can become of mixed type.

Pedigree analysis—Analysis of a family tree, or pedigree, in an attempt to identify the possible inheritance pattern of a trait seen in this family.

Sensorineural hearing loss (SNHL)—Hearing loss that occurs when parts of the inner ear, such as the cochlea and/or auditory nerve, do not work correctly. It is often defined as mild, moderate, severe, or profound, depending upon how much sound can be heard by the affected individual.

Syndromic hearing loss—Hearing loss accompanied by other symptoms that characterize a larger genetic syndrome of which hearing loss is just one of the characteristics.

Vestibular nerve—The nerve that transmits the electrical signals collected in the inner ear to the brain. These signals, and the responses to them, help maintain balance.

childhood hearing impairment is genetically based. Another 20-25% of cases are attributed to environmental factors. The remaining 25-30% of cases are classified as of unknown cause. Some of the cases in this last group are certainly due to non-syndromic genetic causes.

Otosclerosis is estimated to affect between 10% and 18% of all white and Hispanic women and between 7% and 9% of all white and Hispanic men. People of Asian descent are affected with otosclerosis at about half the rate seen in whites and Hispanics, with the same observed sex differences. In African-Americans, only about 1% of the total population is affected with otosclerosis, with minimal differences between males and females. Otosclerosis is exceedingly rare in people of Native American descent.

Accurate demographic figures on the rate of occurrence of DPHL were not available in early 2001. This is because past epidemiological studies of progressive hearing loss have failed to separate DPHL out from the other progressive sensorineural hearing losses.

Signs and symptoms

Syndromic types of hearing loss are generally characterized by the findings and symptoms additional to hearing loss that are associated with the particular syndrome.

Otosclerosis is characterized by an initial loss of hearing in the low frequencies, followed by a loss of the high frequencies, then a loss of the middle frequencies. It may rapidly advance through these stages in some affected individuals, while in others, it may stabilize for a period of years before progressively worsening. Many affected individuals have symptoms only in one ear at first, but otosclerosis almost inevitably will affect both ears. The maximum hearing loss due to otosclerosis without involvement of the auditory nerve is in the moderate range. As an affected person ages and the auditory nerve becomes involved, the hearing loss may progress to severe, or even profound, when this person reaches their 60s and 70s.

There are four main categories of DPHL: early-onset, high frequency, midfrequency, and low frequency. Early-onset types of DPHL tend to occur in early childhood and progress at varying rates to deafness. The other three types are categorized by the frequency range in which hearing loss first occurs.

Diagnosis

Hearing is generally tested using earphones. Sounds are sent into the earphones at various decibel and frequency levels. This test allows the observer to determine the amount of hearing loss in decibels and the range of

hearing loss in hertz. Since hearing loss is not necessarily the same in both ears, each ear is tested independently. If a hearing loss is found using this simple test, another test is then performed to determine whether the hearing loss is of the conductive or sensorineural type. A device called a bone vibrator is used in place of the earphones. The bone vibrator sends auditory signals through the bones of the ear, bypassing the ear canal and the ossicles of the middle ear. In the case of conductive hearing loss, the affected individual will be able to hear sounds at a lower decibel level using the bone vibrator than using the earphones. In the case of sensorineural hearing loss, the affected individual will generally hear sounds through the bone vibrator at the same decibel level as was required using the earphones.

Hearing loss is categorized by determining the hearing threshold of the affected person. The hearing threshold is the amount of sound that that individual can just barely hear. The hearing threshold of an individual is the hearing level (HL) of that person. It is measured in decibels (dB). A person with up to a 25 dB HL is categorized as having "normal" hearing. Mild hearing loss is defined as an HL in the 26 to 45 dB range. Moderate hearing loss is defined as an HL in the 46 to 65 dB range. Severe hearing loss is defined as an HL in the 66 to 85 dB range. Profound hearing loss is defined as an HL greater than 85 dB. The average person speaking English in a conversational tone tends to speak in the 30 to 60 dB range depending on the particular sounds being made. Persons with mild hearing loss will generally be able to hear and understand one-on-one conversations if they are close to the speaker. These individuals may have difficulty hearing a speaker who is far away, has a soft voice, or is surrounded by background noise. Persons with moderate hearing loss may have problems hearing conversational speech, even at relatively close range and in the absence of background noises. Persons with severe hearing loss have difficulty hearing in all situations. These people are not usually able to hear speech unless the speaker is talking loudly and is at relatively close range. Persons with profound hearing loss may not hear loud speech or environmental sounds. These people are unlikely to use hearing and speech as primary means of communication.

Hearing loss is also measured in terms of the frequency of the sounds that can or cannot be heard. Frequency is measured in hertz (Hz). The normal hearing range for humans is from approximately 100 Hz to 8,000 Hz. The normal frequency of the sounds of the English language fall between approximately 240 Hz and approximately 7,500 Hz. In individuals with progressive conductive hearing loss, it is generally the highest frequency range or the lowest frequency range that is lost first; the middle frequency range is generally lost last. In individuals affected with progressive sensorineural hearing loss, it may be any of the three frequency ranges that is lost first.

Hearing loss is generally plotted on a graph called an audiogram. This is a graph of frequency (in Hz) versus HL (in dB).

Syndromic hereditary hearing loss is differentially diagnosed by the presence of the non-hearing loss symptoms that the patient also possesses. Non-syndromic hereditary hearing loss is differentially diagnosed from syndromic by the absence of such other symptoms. Types of non-syndromic hereditary hearing loss are differentially diagnosed by the age of onset of the symptoms; the progressiveness, or non-progressiveness, of the hearing loss; the degree of symmetry of the hearing loss from one ear to the other; and the type of hearing loss: conductive, sensorineural, or mixed. Occasionally, a differential diagnosis also includes the inheritance pattern of the non-syndromic hearing loss. This inheritance pattern is generally determined by obtaining family medical history information on the affected person's family. Tests looking for specific gene changes in specific genes for certain non-syndromic hearing losses, including prenatal testing, are also beginning to become more available.

Treatment and management

Certain types of conductive hearing loss can be treated by surgery to correct the dysfunctional portion of the ear. Sensorineural hearing loss is generally not able to be repaired by surgery.

Most people with partial hearing loss can benefit from the use of hearing aids and/or sign language. Sign language and writing are often the primary forms of communication used by people suffering from severe, profound, or complete hearing loss.

Prognosis

The prognosis for individuals affected with hereditary hearing loss is largely dependent on the type of hearing loss experienced. In the absence of non-hearing loss related symptoms, the loss of hearing does not generally present any increased risk of illness and death. Hearing aids and/or the use of sign language can often improve the quality of life of those affected with a hereditary hearing loss.

Resources

BOOKS

Gorlin, Robert J., Helga V. Toriello, and M. Michael Cohen, Jr., eds. *Hereditary Hearing Loss and Its Syndromes.* Oxford: Oxford University Press, 1995.

ORGANIZATIONS

Boystown National Research Hospital. 555 N. 30th St., Omaha, NE 68131. (402) 498-6749. <http://www.boystown.org/Btnrh/Index.htm>.

League for the Hard of Hearing. 71 West 23rd St., New York, NY 10010. (917) 305-7700 or (917) 305-7999. Fax: (917) 305-7888. <http://www.lhh.org/index.htm>.

National Association of the Deaf. 814 Thayer, Suite 250, Silver Spring, MD 20910-4500. (301) 587-1788. nadinfo@nad.org. <http://www.nad.org>.

WEBSITES

Boystown National Research Hospital. Center for Ear, Hearing and Balance Disorders Fact Sheets. <http://www.boystown.org/btnrh/Deafgene.reg/Facts.htm>.

The Ear Surgery Information Center. <http://www.earsurgery.org/>.

Hearing and Balance Information. <http://www.neurophys.wisc.edu/h%26b/textbook/textindex.html>.

Hereditary Hearing Loss. <http://dnalab-www.uia.ac.be/dnalab/hhh/>.

Heterogeneous Conditions: Nonsyndromic Deafness, DFNB Genes <http://www.ich.ucl.ac.uk/cmgs/deafness.htm>>

Links to Hearing Loss Related Sites. <http://linkage.rockefeller.edu/nshl/hls.html>.

Nonsyndromic Deafness. <http://www.ich.ucl.ac.uk/cmgs/nsdf.htm>.

Paul A. Johnson

Hereditary hemorrhagic telangiectasia (HHT) *see* **Osler-Weber-Rendu syndrome**

Hereditary iron-loading anemia *see* **Anemia, sideroblastic X-linked**

Hereditary multiple exostoses

Definition

Hereditary multiple exostoses (HME) refers to a group of disorders characterized by abnormal bone growth. The major symptom is the development of nodules (bumps) on various bones of the body. Exostoses may produce pain and other complications by pressing on nearby tissue, they may limit movement of joints, and in some cases they must be surgically removed.

Description

An exostosis is a benign (non-cancerous) bony growth. This does not refer to a normally shaped bone that has simply grown larger than normal. Rather, an exostosis is a bump, or nodule, on a bone, usually with overlying cartilage. That is why HME is sometimes referred to as the "bumpy bones" disease. Other names for the disorder include multiple hereditary exostoses (MHE), multiple cartilaginous exostoses, osteochondromatosis, and diaphyseal aclasis.

People with HME typically develop anywhere from several to many exostoses during their life, mostly during childhood and adolescence. Exostoses vary in size, and can develop on most bones in the body. An exostosis may present no problem, or it may cause pain and other complications by pressing on nearby soft tissue (nerves, blood vessels, tendons, internal organs), or on another bone at a joint. Exostoses that do cause problems are often surgically removed. HME can cause differences in the shape of bones, or reduce their growth rate. Thus, people with HME tend to be somewhat shorter than average and may have limited movement in certain joints. People with HME are not at risk for tumor development in other tissues.

HME is an autosomal dominant condition, and most people with the disorder have family members who are affected. A small percentage of people who carry an HME **gene** do not develop any recognizable exostoses. The vast majority of exostoses are benign growths, but a small percentage can become malignant (cancerous).

Genetic profile

Three different types of HME are known to exist—HME type I, HME type II, and HME type III. There appear to be no obvious differences in the presentation and course of the disorder between the three types. Instead, the designations correspond to the three genes—EXT1, EXT2, and EXT3 respectively—that have been linked to HME. The protein produced by the EXT1 gene on chromosome number 8 is called exostosin-1, and the EXT2 gene on chromosome number 11 produces exostosin-2. The EXT3 gene is located on chromosome number 19, but as of 2000, its protein product had not been identified.

As noted, HME is an autosomal dominant condition, which means any person who carries an HME gene has a 50% chance of passing it on each time they have a child. Ninety percent of people with HME have a positive family history. In the other 10% of cases, HME occurred in that person for the first time as the result of a new mutation in one of the EXT genes. Regardless of whether someone inherits HME from a parent or it occurs in them for the first time, each of their children is still at 50% risk.

A tumor is the result of cells that undergo uncontrolled replication/division. People often equate the word "tumor" with **cancer**. However, a tumor is simply a growth, and may be malignant (cancerous) or benign

(non-cancerous). Technically exostoses are tumors, but they are nearly always benign.

EXT1 and EXT2 belong to a class of genes known as tumor suppressors. In normal circumstances, tumor suppressor genes prevent cells either from replicating at all, or from replicating too quickly. If both copies of a tumor suppressor gene are mutated (inactivated), control of cell replication/division is lost. A person who inherits HME type I or HME type II already has one EXT1 or EXT2 gene inactivated from the moment they are conceived. However, abnormal bone growth does not occur unless the other gene of the pair also becomes inactivated. This second **gene mutation**, called loss of heterozygosity (LOH), appears to be an unlikely, random event, which explains why there is not abnormal growth throughout all of the bones. Only the occasional bone cell that undergoes LOH has a chance of becoming an exostosis. Any person without HME can develop a single exostosis, and 2% of all people do. It is simply that exostosis development is much less likely when two random mutations of an EXT gene in a bone cell must occur, rather than just one.

Demographics

The prevalence of HME is estimated at about 1 in 75,000. There does not appear to be any significant difference in prevalence between the major ethnic groups. Most studies have found that males with an HME gene tend to have more obvious and severe symptoms than females. The reason for this is unknown. This makes it appear as though males are more likely to inherit HME, when in fact they are just more likely to be diagnosed.

Most people with HME have either HME type I or HME type II. Apparently only a small percentage of HME cases are linked to the EXT3 gene. Further study of the HME genes should establish an accurate prevalence for each type.

Signs and symptoms

About half of all people with HME are diagnosed by the time they are three years old. Only 5% of newborns that carry an HME gene show some signs at birth, but 95% of all people with the condition show noticeable signs by the time they are 12 years of age.

Exostoses primarily develop during the period of rapid bone growth—from infancy through late adolescence. As noted, however, a small percentage of newborns already have noticeable exostoses at birth, and rare individuals with HME may develop exostoses as adults. The number of exostoses varies from person to person, even within families. However, the average affected person develops six exostoses during his or her life.

KEY TERMS

Chondrosarcoma—A malignant tumor derived from cartilage cells.

Diaphysis—The middle portion, or shaft, of a long bone.

Epiphysis—The end of long bones, usually terminating in a joint.

Exostosis—An abnormal growth (benign tumor) on a bone.

Metaphysis—An area of softer bone and cartilage in long bones between the diaphysis (shaft) and epiphysis (end).

Osteochondromatosis—Another name for hereditary multiple exostoses, meaning a growth of bone and cartilage.

Both the locations and sizes of exostoses vary. The most commonly affected bones are those of the arms (humerus, radius, and ulna), legs (femur, tibia, and fibula), hands (carpals and metacarpals), and feet (tarsals and metatarsals). Exostoses on the arm or leg nearly always develop near the joints (elbow, wrist, knee, or ankle), rather than in the middle of the long bones. About 70% of people with HME have an exostosis or bone deformity around the knee. Flat bones, such as the scapula (shoulder blade) and pelvis, may be affected. The ribs and bones of the shoulder girdle occasionally develop growths, but exostoses are hardly ever seen on the spine or bones of the skull. Some exostoses under the skin may be barely noticeable to the touch (less than 1 cm in height), while others produce a noticeable bump (1-2 cm in height). Growths on the flat bones may be somewhat larger.

The most common problem in HME is exostoses that cause compression and irritation of adjacent soft tissue, such as skin, nerves, and blood vessels. These types of growths can cause chronic pain until they are removed, and accidentally hitting them against something solid can be especially painful. Exostoses that grow near the ends of long bones may interfere with normal movement of a joint. Many children with HME have difficulties with their knees, both in range-of-motion and with angular deformities ("knock-kneed"). An uncommon, but more complicated problem is a large exostosis on the inside of the pelvis that results in compression of the intestine or urinary tract.

HME affects the growth centers of bones (metaphyses and epiphyses), which can result in abnormal modeling (structure) of the affected bones. Reduction in size and bowing of bones are the most frequent structural anomalies seen. Consequently, people with HME tend to be somewhat shorter than average—final height in men averages 170 cm (66 in), while the average height in women is 160 cm (62 in). Differential rates of growth between a child's legs or arms can result in leg- or arm-length discrepancy, sometimes reaching 2 cm (1 in) or more. Leg-length discrepancy can result in hip pain and problems with walking caused by tilting of the pelvis.

The most serious complication in HME is the progression of a benign exostosis to a malignant (cancerous) state, known as a **chondrosarcoma**. This happens in slightly less than 1% of all people with the condition. Chondrosarcomas can develop in children, but those few cases that do occur are usually in adults. An undetected bone malignancy always presents a risk for metastasis—spreading of cancerous cells elsewhere in the body—which is one of the most dangerous complications of any cancer. Most chondrosarcomas should be detected and treated early, however, because they are usually associated with rapid growth of an exostosis accompanied by pain.

Diagnosis

The diagnosis of HME is usually made when noticeable exostoses first appear. Any person who is at risk for the condition because of a family history is more likely to be accurately diagnosed at a younger age. As noted, the occurrence of a single exostosis in an otherwise healthy person is not rare. Therefore, two or more exostoses must be present in order to make the diagnosis of HME (although a single exostosis detected in someone who is known to be at 50% risk for HME is highly suggestive of the diagnosis).

Exostoses are not always detectable by physical examination. Consequently, an x-ray study of the commonly affected bones (skeletal survey) in questionable cases is the best method of confirming or excluding the diagnosis. This is especially true in cases where a child is known to be at risk for HME (positive family history).

Unlike some **genetic disorders** where many people with the condition have the same gene mutation, most individuals/families with HME tested so far have had different mutations in either EXT1 or EXT2. Therefore, while predictive or confirmatory **genetic testing** might be possible within a family (assuming the gene mutation is detectable), direct testing of EXT1/EXT2 in a person with a negative or uncertain family history is not yet reliable enough to use as a diagnostic tool.

Treatment and management

The only treatment for exostoses that present problems is to remove them surgically. In those instances where the exostosis is easily accessible, surgical removal is straightforward and carries very little risk. On the other hand, an exostosis that involves one of the joints or is less accessible—somewhere on the inner surface of the pelvis, for instance—may require involved surgery. A few people with HME will never require surgical intervention, but most have at least one surgery and some will have many. A child who is noted to have uneven or accelerated growth of a long bone in the arm or leg may be offered a procedure to straighten the bone or reduce its growth rate.

No external factors are known to cause or prevent the growth of exostoses. Those persons diagnosed with HME, as well as children at risk, must be taught to monitor themselves for unusual changes in bone growth.

Anyone with HME should have lifelong, periodic examinations by an orthopedic surgeon to look for and address any problematic exostoses, and to screen for chondrosarcoma. Since exostoses and other bone-growth problems occur primarily in childhood, special attention, care, and education about their disorder is often needed for children with HME. A support group especially for children, called MHE and Me, has special materials and a Web site devoted to issues of particular importance to kids (see Resources below).

Prognosis

The majority of people with HME lead active lives, and their lifespan is not reduced. Surgery to remove problematic exostoses will likely remain the primary method of treatment for some time. The hope is that further analysis of the EXT genes and their protein products will lead at some point to a more targeted approach at reducing or eliminating abnormal bone growths altogether.

Resources

ORGANIZATIONS

MHE and Me—A Support Group for Kids with Multiple Hereditary Exostoses. 14 Stony Brook Dr., Pine Island, NY 10969. (914) 258-6058. <http://www.geocities.com/mheandme>.

Multiple Hereditary Exostoses Coalition. 8838 Holly Lane, Olmstead Falls, OH 44138. (440) 235-6325. <http://www.radix.net/~hogue/mhe.htm>.

Multiple Hereditary Exostoses Family Support Group. 5316 Winter Moss Court, Columbia, MD 21045. (410) 922-5898. <http://www.radix.net/~hogue/mhe.htm>.

Scott J. Polzin, MS, CGC

Hereditary nonspherocytic anemia *see* **Pyruvate kinase deficiency**

Hereditary nonspherocytic hemolytic anemia *see* **Pyruvate kinase deficiency**

Hereditary pancreatitis

Definition

Hereditary pancreatitis is a rare genetic condition beginning in childhood that is characterized by recurrent episodes of inflammation of the pancreas, causing intense abdominal pain, nausea and vomiting. Most episodes resolve on their own, but serious complications can arise, ranging from diabetes and poor digestion, to bleeding, infection, pancreatic cancer and death. Medical treatment can help alleviate some of the symptoms, and occasionally surgery may be needed to treat some of the complications.

Description

The pancreas is an organ located in the abdomen that has several functions. First, the pancreas aids in the digestion of food through the production of digestive enzymes. Digestive enzymes are proteins that break down food components, including sugars, fats, and other proteins, so that they can be absorbed and used by the body. Normally, the digestive enzymes are stored within the pancreas in an inactive form. In response to food intake, the enzymes are released from the pancreas and travel through the pancreatic duct into the small intestine where they become activated and begin to digest food.

The second function of the pancreas is to maintain proper sugar balance in the blood. The pancreas produces several hormones, including insulin and glucagon, that are secreted into the bloodstream and act to increase or decrease sugar levels within the blood.

Pancreatitis is a condition in which the pancreas becomes irritated and inflamed. In most cases, the condition is caused by excessive alcohol use, or by the presence of gallstones, but can also be caused by medications, viral infections, injury to the abdomen, abnormal structures of the pancreas, and several metabolic disorders. In some rare instances, pancreatitis is caused by a genetic abnormality that is passed down from parent to child and is called hereditary pancreatitis.

In hereditary pancreatitis, an individual inherits a genetic abnormality in one of the digestive enzymes produced by the pancreas, called trypsin. Normally, trypsin is stored within the pancreas in an inactive state, and only becomes activated when it travels to the small intestine and encounters food to digest. However, in individuals with hereditary pancreatitis, the trypsin becomes activated while still in the pancreas and begins to digest the pancreas itself, causing irritation and inflammation. Damage to the blood vessels in the pancreas can result in bleeding or fluid leaks from the blood vessel into the abdominal cavity. The digestive enzymes also gain access to the bloodstream through the damaged blood vessels, and begin circulating throughout the body, causing further damage.

It is unclear what causes the abnormal trypsin enzyme to become activated and begin digesting the pancreas, but some studies have shown that emotional stress, alcohol, or fatty foods may trigger the process. After time, recurrent episodes of pancreatitis may leave the pancreas permanently irritated and damaged, a condition called chronic pancreatitis.

Genetic profile

Hereditary pancreatitis is a genetic disease and can be inherited or passed on in a family. The genetic abnormality for the disorder is inherited as an autosomal dominant trait, meaning that only one abnormal **gene** is needed to inherit the disease, and that a parent with the disease has a 50% chance of transmitting the abnormal gene and disease to a child.

Changes in the gene for the digestive enzyme trypsin (located on human chromosome 7, at 7q35) are responsible for the disease, and more than five different genetic changes in the trypsin gene have been identified. Changes in other genes may also cause hereditary pancreatitis, as recent studies have discovered families with this condition with mutations in other genes, possibly on chromosome 12.

Demographics

The annual incidence of all forms of pancreatitis is about one per 10,000 people. However, hereditary pancreatitis is a rare cause of all pancreatitis and comprises only about 2% of the total cases. While the true prevalence of the condition is difficult to measure, it is estimated that at least 1,000 individuals in the United States are affected by hereditary pancreatitis.

Approximately 100 different families with hereditary pancreatitis have been identified since the condition was first recognized in 1952. The largest concentration of hereditary pancreatitis in the United States is in the central Appalachian region, which extends from southern Ohio to eastern Kentucky and

KEY TERMS

Abscess—A localized collection of pus or infection that is walled off from the rest of the body.

Amylase—A digestive enzyme found in saliva or pancreatic fluid that breaks down starch and sugars.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Diabetes—An inability to control the levels of sugar in the blood due to an abnormality in the production of, or response to, the hormone insulin.

Digestive enzyme—Proteins secreted by the pancreas that enter the small intestine and break down food so it can be absorbed by the body.

Gastroenterologist—A physician who specializes in disorders of the digestive system.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Intravenous—A route for administration of fluids, nutrients, blood products, or medications. A small, flexible plastic tube is inserted into a vein by way of a needle to establish this route.

Lipase—A digestive enzyme found in pancreatic fluid that breaks down fats.

Nasogastric tube—A long flexible tube inserted through the nasal passageways, down the throat, and into the stomach. Used to drain the contents of the stomach.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Pseudocyst—A fluid-filled space that may arise in the setting of pancreatitis.

Ranson criteria—A system of measurements, including age and blood testing, that can be used to predict the outcome of a person who has been hospitalized for an episode of pancreatitis.

Shock—An inability to provide the body with the oxygen it requires, sometimes due to large amounts of bleeding or fluid loss.

Trypsin—A digestive enzyme found in pancreatic fluid that breaks down proteins. This enzyme is abnormal in hereditary pancreatitis.

Tennessee, western Virginia and North Carolina, and into northern Georgia.

Signs and symptoms

Hereditary pancreatitis begins with recurrent episodes of pancreatitis during childhood. The age of the first episode of pancreatitis may range from infancy to over 30 years old, but 80% of patients will show the first episode of pancreatitis before 20 years old, and the average individual shows a first episode at approximately 10 to 12 years old.

People who are experiencing an episode of pancreatitis have severe abdominal pain, nausea and vomiting that is greatly worsened by eating. The pain is often described as steady and dull pain that is centered on the navel and may extend to the back. As a result of fluids that leak from the pancreas and surrounding vessels into the abdomen, the abdomen may swell.

The severity and duration of each episode may range from only occasional abdominal discomfort to prolonged, life-threatening attacks that appear to last for weeks. The number of attacks is also quite variable. For example, severe attacks may occur three or four times in a year followed by a year without attacks.

Most episodes of pancreatitis resolve without problems. However, certain complications can arise which may worsen the condition and threaten the life of the patient. Because of the loss of large amounts of fluid into the abdomen, circulatory shock may occur. Shock occurs when fluid leaks from blood vessels, leaving an insufficient amount of blood volume to provide the body with the oxygen that it needs. Prolonged lack of appropriate levels of oxygen causes damage to many different organs of the body. If not immediately treated, shock can lead to death.

Another complication of pancreatitis is the development of a fluid collection that contains decaying products

of an inflamed pancreas and other substances. This fluid collection is called a pseudocyst. A pseudocyst can become life threatening if it becomes infected (abscess) or if the fluid collection ruptures into the abdomen.

Other dangerous and life-threatening complications of pancreatitis include severe bleeding from the pancreas (hemorrhagic pancreatitis), higher risk for the formation of blood clots, and a higher risk of serious infections in the abdomen or damaged pancreas. In addition, people with hereditary pancreatitis have a much higher risk of developing **pancreatic cancer**, for reasons that are not clear. Studies indicate that people with hereditary pancreatitis are at least 53 times more likely to develop pancreatic cancer than the general population and that 40-75% of people with hereditary pancreatitis will develop pancreatic cancer by the age of 70. Pancreatic cancer is very difficult to treat and is nearly always fatal.

Over time, recurrent episodes of pancreatitis may leave the pancreas permanently damaged and unable to carry out its routine functions. The absence of digestive enzymes normally secreted by the pancreas results in poor digestion, chronic diarrhea, weight loss, and malnutrition (5-45% of people), leaving a person generally weakened. The pancreas may also become unable to secrete insulin in the bloodstream normally, creating imbalances in blood sugar and causing diabetes in 10-25% of people with hereditary pancreatitis.

Diagnosis

Hereditary pancreatitis is diagnosed through a combination of medical history, physical examination, and laboratory testing. The onset of abdominal pain consistent with pancreatitis before the age of 20 in multiple family members without any other risk factor for pancreatitis (drinking large amounts of alcoholic beverages; gallstones) suggests a diagnosis of hereditary pancreatitis. The medical history and physical examination of these individuals during an episode of pancreatitis will show abdominal pain, nausea, vomiting, and abdominal swelling.

Diagnosis of pancreatitis can be made by noting high levels of pancreatic enzymes (amylase and lipase) circulating in the blood. Further abnormalities in the blood that suggest pancreatitis include: increased white blood cells, changes in the blood substances that occur with dehydration and fluid loss, and decreases in calcium levels.

Other diagnostic methods can be used to track the progress of the disease and monitor for any complications. X rays of the abdomen may show deposits of calcium that occur in 50% of cases of hereditary pancreatitis. Also, the intestines may show signs of inactivity because of the nearby inflammation. Computed tomography scans (CT scans) of the abdomen may reveal the inflammation of the pancreatitis, and are very useful in monitoring for complications such as pseudocyst, infections, and bleeding.

Genetic testing allows for the definitive diagnosis of hereditary pancreatitis by identifying abnormalities in the trypsin gene. However, these tests are currently used only for research purposes and are not generally available.

Treatment and management

There is no cure for hereditary pancreatitis. The goals for treatment consist of pain control, establishing alternate routes of feeding and fluid administration, and prevention or control of complications.

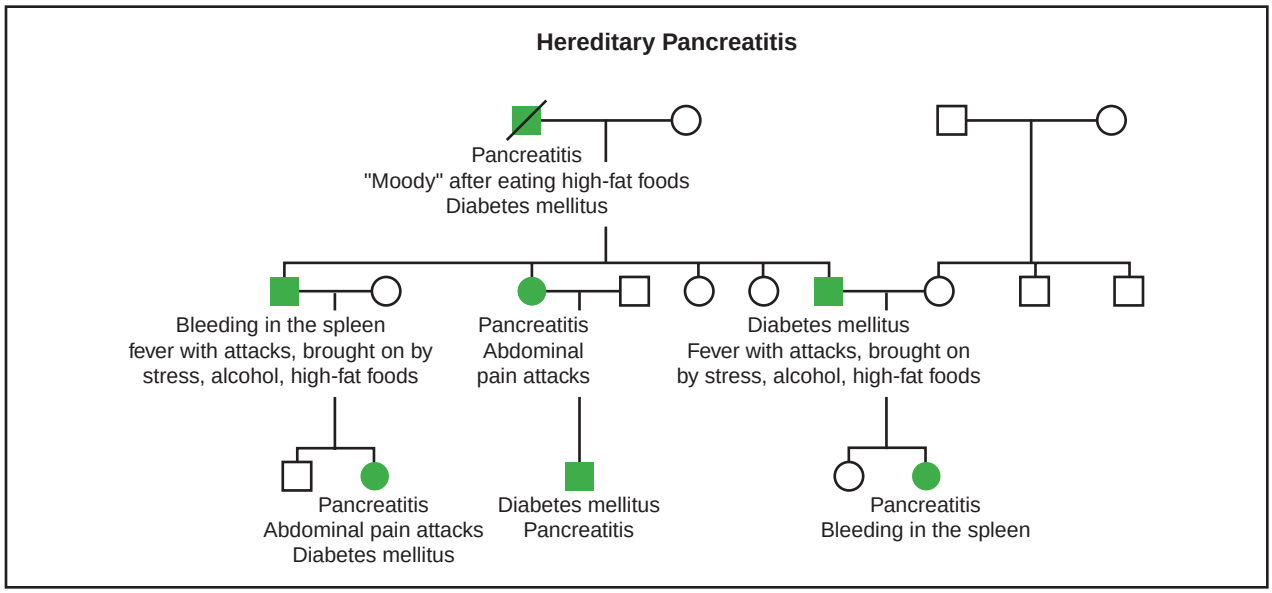
A person experiencing an episode of pancreatitis is nearly always admitted to the hospital for treatment. Since drinking or eating by mouth often worsens the patient's condition, alternative routes are needed. Large amounts of fluid are given by a small tube placed in a vein (intravenous or IV fluids) to replace the fluid that has leaked into the abdomen. This IV route can also be used to administer nutritional products and medications to relieve pain.

Fluids and acid that are produced by the stomach can worsen a patient's condition and increase pain. In order to drain these fluids, a small, flexible tube is inserted through the nose, down the throat and into the stomach (nasogastric tube). The tube is then connected to a weak vacuum to remove the contents of the stomach. Complications may arise in the setting of pancreatitis. Bleeding may require administration of donor blood products by vein, while infections are treated using antibiotics also given by vein. Abscesses, large pseudocysts or decaying portions of the pancreas may require drainage with a needle or need to be removed surgically. People with a permanently damaged pancreas may require digestive enzyme supplements by mouth to assist with digestion and insulin injections to control diabetes.

People diagnosed with hereditary pancreatitis should be seen regularly by a team of health care professionals, including a primary-care physician, gastroenterologist, and medical geneticist. Individuals with this condition should refrain from drinking alcohol and avoid fatty foods and may benefit from consultation with a licensed nutritionist.

Prognosis

Several systems have been developed to predict the outcome for people who are experiencing an episode of pancreatitis. The most widely used system utilized by health professionals is called "Ranson criteria," which utilizes a list of measurements that are determined during the first two days of the hospital stay.



(Gale Group)

In general, children who experience an episode of pancreatitis do well and are released from the hospital in three to five days. However, the development of any of the complications of pancreatitis discussed above worsens the prognosis and will likely result in a longer hospital stay. In the extreme, severe complications of pancreatitis can even lead to death.

Most people with hereditary pancreatitis will develop permanent damage to the pancreas as they grow older. Half of people will require surgery, and up to one-fourth will develop diabetes by the age of 70. Of even greater concern, a significant percentage will develop pancreatic cancer, a diagnosis that is nearly always fatal within several years.

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Oren Traub, MD, PhD

Hereditary spastic paraplegia

Definition

Hereditary spastic paraplegia (HSP) is a varied group of disorders, all primarily involving subtly progressing lower extremity muscle weakness and spasticity, or increased muscle reflexes.

Description

There are two primary groups of HSP, known as "uncomplicated" or "pure" HSP and "complicated" HSP. HSP is considered "uncomplicated" or "pure" if the neurological problems only include progressive lower extremity muscle weakness and spasticity, urinary bladder disturbances, a decreased ability to sense vibrations in the lower extremities, and a decreased ability to sense the position of the joints.

HSP is "complicated" if other complex problems are present such as seizures, **dementia**, loss of muscle mass, mental delays, dry and thick skin (**ichthyosis**), vision problems or loss, and ataxia.

Problems with gait may progress over years or decades in uncomplicated HSP. This finding may begin at any age, from early childhood through late adulthood. The problems are usually limited to the lower extremities (legs and feet). Occasionally, urinary bladder disturbances may develop over time. People with complicated HSP have other associated health problems including mental delays and dementia.

Alternate names for HSP include hereditary spastic paraparesis, familial spastic paraplegia, familial spastic paralysis, and Stumpell-Lorrain syndrome.

Genetic profile

HSP is a genetically diverse group of disorders. It can be inherited in autosomal dominant or autosomal recessive manners; these are further divided into uncomplicated and complicated groups. An X-linked recessive form also exists for complicated HSP. The genes for HSP are designated "spastic gait" (SPG) genes, and are numbered 1–13 in order of their discovery. Determination of the exact type of HSP in a family is usually done by a detailed family history, rather than **genetic testing**.

In autosomal recessive HSP, individuals may be carriers, meaning that they carry a copy of an altered **gene**. However, carriers often do not usually have symptoms of HSP. Those affected with autosomal recessive HSP have *two* copies of an altered gene, having inherited one copy from their mother, and the other from their father. Thus, only two carrier parents can have an affected child. For each pregnancy that two carriers have together, there is a 25% chance for them to have an affected child, regardless of the child's gender. In families with autosomal recessive HSP, one would not expect to find other affected family members in past generations.

Autosomal recessive uncomplicated HSP is thought to represent about 25% of inherited spastic paraplegia. The SPG5 gene (found on chromosome 8 at 8p11–8q13) and SPG11 gene (on the long arm of chromosome 15 at 15q13–q15) appear to be responsible for this group of HSP. Autosomal recessive complicated HSP has been associated with alterations in the SPG7 gene (on the long arm of chromosome 16 at 16q24.3). Additionally, a gene named the paraplegin gene has been identified at the SPG7 locus. Although its function is not well understood, alterations in this gene appear to be responsible for autosomal recessive complicated HSP.

In autosomal dominant HSP, an affected individual has one copy of a genetic alteration that causes HSP. The individual has a 50% chance to pass the alteration on to each of his or her children, regardless of that child's gender. There are often other affected family members in prior generations, and often a parent is affected.

As of 2000, seven genes have been attributed to autosomal dominant uncomplicated HSP. The uncomplicated form comprises about 80% of families with autosomal dominant HSP. They are: SPG3 (found on the long arm of chromosome 14 at 14q11–q21), SPG4 or spastin (short arm of chromosome 2 at 2p22), SPG6 (long arm of chromosome 15 at 15q11.1), SPG8 (long arm of chromosome 8 at 8q23–q24), SPG10 (long arm of chromosome 12 at 12q13), SPG12 (long arm of chromosome 12 at 19q13), and SPG13 (long arm of chromosome 2 at 2q24–q34). Of this group, about 45% of families have SPG4 or spastin alterations.

Autosomal dominant complicated HSP has been attributed to alterations in the SPG9 gene (on the long arm of chromosome 10 at 10q23.3–q24.2).

In X-linked recessive HSP, only males are affected with the condition, because the genetic alterations are found on the X-chromosome. Males have only one X-chromosome, and females have two. Males with an X-linked condition have the genetic alteration on their single X-chromosome, and they develop symptoms of the condition. Females are carriers, and typically do not have symptoms. However, when carrier females have sons, they have a 50% chance of having an affected son. In families with X-linked HSP, males are affected and it is passed through women in the family.

X-linked forms of HSP are complicated HSP. The SPG1 gene on the long arm of chromosome X at Xq28 (also known as the L1 cell adhesion molecule) and SPG2 gene on Xq28 (also known as the proteolipid protein) have been associated with this form of HSP. Specifically, proteolipid protein alterations cause a condition known as **Pelizaeus-Merzbacher disease**.

Demographics

HSP is relatively rare; through 1996 more than eighty unrelated families had been studied throughout the world. Hereditary spastic paraplegia appears to affect individuals and various age groups around the world. With the exception of X-linked recessive HSP, it affects men and women equally.

Signs and symptoms

The symptoms of uncomplicated HSP may appear at any age. It may progress very slowly, without any obvi-

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

Gait—A manner of walking.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Paraplegia—Loss of voluntary movement and sensation of both lower extremities.

Paresthesia—An abnormal sensation resembling burning, pricking, tickling, or tingling.

Spasticity—Increased mucle tone, or stiffness, which leads to uncontrolled, awkward movements.

ous changes to bring symptoms to medical attention, possibly appearing as general "clumsiness." Individuals with uncomplicated HSP often have no problems with strength in their upper extremities and no problems with speech, chewing, or swallowing. They may notice their leg muscles becoming very stiff, and may stumble when climbing stairs or crossing curbs. These symptoms can progress and worsen with time.

Each family with HSP is unique, with varying symptoms. Additionally, affected individuals within the same family may have varying presentations of the disease. In 1999, a family was reported in which individuals in successive generations had increasingly severe symptoms of pure HSP, a phenomenon known as "genetic anticipation." People with pure HSP may experience difficulty walking and often eventually require canes, walkers, or wheelchairs. As a later symptom, people may experience an urgency to urinate, or may have problems with urinary control. Generally, the lower extremities experience increased reflexes, and may become stiff.

Individuals with complicated HSP still have spastic paraplegia of the lower extremities as a common finding, but may also experience other associated health problems. These may include seizures, mental delays, vision loss, and loss of muscle mass. Cataracts, gastric reflux, abnormal eye movements, severe general muscle weakness, and ataxia can also be present.

For some forms of complicated HSP, specific syndromes have been identified. Silver syndrome is an autosomal dominant condition involving progressive spastic paraplegia and loss of muscle mass, particularly in the hands. Pelizaeus-Merzbacher disease is an X-linked recessive form of complicated HSP. It usually develops in infancy or early childhood with abnormal eye movements, severe muscle weakness, feeding problems, and developmental delays. These findings can progress to include severe muscle spasticity and ataxia.

Diagnosis

HSP has classically been diagnosed by a careful physical examination, as well as obtaining a detailed personal and family medical history. Other similar disorders often need to be ruled out before considering HSP. Uncomplicated HSP is diagnosed by four clinical criteria:

- Clinical symptoms: Progressive spastic muscle weakness of both lower extremities, often with urinary urgency or lower extremity paresthesia.
- Neurologic examination: Increased muscle tone/reflexes at the hamstrings, quadriceps, and ankles; muscle weakness at hamstrings and lower limbs; decreased ability to sense vibrations in the lower limbs; abnormal gait with an uneven drop of the foot. (Mental delays or dementia are not expected in pure HSP.)
- Family history: Similar to an autosomal dominant pattern (several affected family members in different generations), autosomal recessive pattern (siblings may be affected but little or no history of affected family members in prior generations), or X-linked recessive pattern (primarily affected males who are related to each other through their mothers).
- Exclusion of other conditions.

Magnetic resonance imaging (MRI) of the brain and spinal cord are usually normal in people with uncomplicated HSP. It is a difficult task to eliminate other neurologic disorders with symptoms similar to HSP, such as structural abnormalities of the brain or spinal cord. Multiple sclerosis often includes gait incoordination, but it does not always progress or worsen with time. Some other genetic conditions involving muscle weakness include various forms of leukodystrophy; however, these neurological problems may progress rapidly, and may even result in death. Some infectious diseases may in some ways mimic HSP, such as AIDS or syphilis.

Genetic testing for some forms of both pure and complicated HSP is available on a research basis. In these cases, testing is usually performed on a blood sample, and the genes are analyzed. Because the testing is considered experimental research, testing may be cost-free but results may not always be available to the family.

For Pelizaeus-Merzbacher disease, genetic testing is available on a clinical basis at a limited number of laboratories, and families receive their results. In this case, results would be considered abnormal if alterations in the proteolipid gene were identified. Because Pelizaeus-Merzbacher disease is an X-linked recessive disorder, any male with the alteration would always have carrier daughters and unaffected sons. The affected person's mother would then be a carrier, and risks to her family members could be predicted by the same form of testing. An exception to this would be in the case of some mothers of boys with PLP mutations who are not carriers because their sons have new mutations.

Prenatal testing for Pelizaeus-Merzbacher disease can be performed on **DNA** extracted from fetal cells obtained through **amniocentesis** or chorionic villus sampling (CVS).

Treatment and management

There is no specific treatment to prevent, slow, or reverse the progressive symptoms in HSP. Some treatment approaches for other patients with paraplegia have been useful. This includes oral and muscle injections of a medication known as Baclofen, which can be used in early stages of muscle weakness. A medication known as Oxybutynin has been helpful for the urinary disturbances. Physical therapy and exercise are considered important elements in maintaining muscle strength and range of motion. However, it is still unclear whether physical therapy promotes muscle improvement or reduces the rate of muscle weakness and decline.

Prognosis

Complicated HSP may be associated with a shortened lifespan, because involvement of other health problems can worsen an individual's prognosis. For example, in Pelizaeus-Merzbacher disease, lifespan is shortened because the associated severe muscle weakness and feeding problems for a young child may lead to early death. Though it is usually very physically disabling, uncomplicated or pure HSP does not typically shorten lifespan.

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National Ataxia Foundation. 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447. Phone: (763) 553-0020. Fax: (763) 553-0167. naf@mr.net. <http://www.ataxia.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (800) 999-6673 or (203) 746-6518. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Deepti Babu, MS

Hermansky-Pudlak syndrome

Definition

Hermansky-Pudlak syndrome (HPS) is a rare inherited disorder of melanin production. Melanin is the pigment that gives color to the skin, hair, and eyes. A lack or decrease of pigment in the skin and eyes is called oculocutaneous **albinism**. HPS is a specific type of oculocutaneous albinism that also includes a bleeding tendency

KEY TERMS

Bioptics—Glasses that have small telescopes fitted in the lens.

Ceroid—The byproduct of cell membrane breakdown.

Colitis—Inflammation of the colon.

Cytoplasm—The substance within a cell including the organelles and the fluid surrounding the nucleus.

Diarrhea—Loose, watery stool.

Melanin—Pigments normally produced by the body that give color to the skin and hair.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nystagmus—Involuntary, rhythmic movement of the eye.

Oculocutaneous albinism—Inherited loss of pigment in the skin, eyes, and hair.

Organelle—Small, sub-cellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

Photophobia—An extreme sensitivity to light.

Sputum—A mixture of saliva and mucus from the lungs.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

and the storage of ceroid, the byproduct of cell membrane breakdown, in the body's cells.

Description

In 1959, Drs. F. Hermansky and P. Pudlak reported two unrelated people with oculocutaneous albinism who had lifelong bleeding problems. The female died at age 33, and at that time large amounts of pigment were discovered in the walls of her small blood vessels.

Genetic profile

HPS is an autosomal recessive disorder. This means that the disease manifests itself when a person has inherited one nonworking copy of the HPS **gene** from each parent. Parents who carry the gene for HPS are healthy and have typical skin pigmentation. However, each time they have a child, the chance for the child to have HPS is 25%, or 1 in 4. Unless someone in the family has HPS, most couples are unaware of their risk.

Researchers mapped the HPS1 gene to the long arm of chromosome 10 in 1995, and later identified its exact location in 1996. The protein produced by the HPS gene helps organelles (specialized parts) of the cell's cytoplasm (portion of the cell between the membrane and nucleus) to develop and function normally.

In 1999, another group of researchers identified a mutation, or gene change, in the AP3B1 gene located on chromosome 5 as another cause of HPS. This gene makes AP3, a molecule that helps to sort proteins within the body's cells.

Demographics

In northwest Puerto Rico, HPS is a common inherited disorder. More than 300 persons are affected. The carrier rate is about one in 21. Intermarriage accounts for the high frequency. Researchers have traced the origin of HPS to southern Spain. Cases have also been reported in the Dutch, Swiss, and Japanese. Both sexes are equally affected. However, females will have more lung symptoms than males.

Signs and symptoms

People with HPS have a broad range of skin color from tan to white, reflecting the partial absence of pigmentation. Hair color ranges from brown to white, also reflecting how much pigmentation is present.

Poor vision and eye abnormalities are common in people with HPS. Visual acuity can approach 20/200. Nystagmus, an irregular rapid back and forth movement of the eyes, is also common. The eyes can have an improper muscle balance called strabismus. Sensitivity to bright light and glare, known as photophobia, is a frequent complaint of people with HPS. These visual problems all result from abnormal development of the eye due to the lack of pigment. Just as skin and hair color vary, so will eye color. Red, brown, hazel, and violet eyes have been reported.

A bleeding tendency distinguishes HPS from other types of albinism. People with HPS will bruise easily and bleed for an extended time after dental extractions and surgical procedures. Platelets are the disc-shaped structures in the blood that cause clotting. In people with HPS, the platelets are missing certain internal components that cause them to clump together during the clotting process.

The third finding of HPS is the accumulation of ceroid in certain cells of the body such as bone marrow

and the lung. As ceroid collects in the lungs, it makes the affected individual prone to respiratory infections and progressive lung disease that restricts breathing. Some people also complain of colitis (an inflammation of the colon) and diarrhea (loose, watery stools).

Diagnosis

Diagnosis of HPS can be made by specialized platelet testing and molecular testing for the known gene mutations. Very few laboratories are equipped to perform these tests. A person who is suspected to have HPS should consult with a geneticist or genetic counselor to arrange for the appropriate tests. Molecular testing is available for Puerto Rican families who usually have a specific detectable gene alteration, which is a duplication of a small segment of the gene.

Analysis of the person's platelets will determine if they are lacking the critical internal parts, called dense bodies, that help to clot blood. If dense bodies are not present, then HPS is the diagnosis.

For affected people of Puerto Rican ancestry, one unique **gene mutation** is present. Several other mutations can also be detected, but the lack of a gene mutation does not mean a person does not have HPS, since all mutations have not been identified.

For some families with an affected child, prenatal diagnosis may be possible for future pregnancies. Parents should consult with a genetics specialist when planning a pregnancy.

Treatment and management

For the individual with HPS, vision problems are always present. Many people will meet the legal definition of blindness, but still have enough vision for reading and other activities. Other affected people may be far-sighted or near-sighted.

An ophthalmologist, a specialist for the eyes, will help those individuals who have strabismus, a muscle imbalance in the eyes. They can have corrective surgery that will not only improve their physical appearance but also expand their visual field. Surgery, however, cannot restore pigment to the eyes nor correct the optic nerve pathways leading from the brain to the eyes.

Many optical aids can help a person with HPS function better in daily life. Aids like hand-held magnifiers, strong reading glasses, and glasses that have small telescopes fitted in the lens called bioptics can make hobbies, jobs, and other activities easier.

Protection from excessive sunlight is crucial for people with HPS. Sunscreens of the highest rating should be used to decrease the chance for fatal skin cancers. By wearing clothing that blocks as much sunlight as possible, people with HPS can enjoy outdoor activities. A dermatologist, a specialist in skin disorders, can examine the affected person if any changes in skin color or appearance occur. Annual skin check-ups are important.

As people with HPS reach their 30s, they begin to have lung disease. The first sign is difficulty in breathing, followed by a cough that does not bring up sputum, a mixture of saliva and mucus, from the lungs. Gradually, the lungs develop a tough, fibrous tissue that further limits breathing. The inability to breathe is the most common cause of death for people with HPS.

Prolonged bleeding after tooth extraction, nosebleed, or surgery occurs regularly in people with HPS. Before any surgery, treatment with desmopressin, a drug that stimulates clotting activity, can be effective. Also, individuals with HPS should avoid aspirin, because it makes blood less likely to clot.

Prognosis

Many people with HPS may have concerns about their physical appearance and decreased vision. Education about the disorder is important to prevent isolation and stigmatization. Once the visual difficulties are addressed, people with albinism can participate in most activities.

Although many preventive efforts can improve the quality of life for a person with HPS, the progressive lung disease cannot be halted. The inability to breathe generally becomes fatal when the affected person is 40–50 years old.

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Hermansky-Pudlak Syndrome Network. 39 Riveria Court, Malverne, NY 11565-1602. (800) 789-9477 or (516) 599-2077. <http://www.medhelp.org/web/hpsn.htm>.

National Organization for Albinism and Hypopigmentation. 1530 Locust St. #29, Philadelphia, PA 19102-4415. (215) 545-2322 or (800) 473-2310. <http://www.albinism.org/infobulletins/hermansky-pudlak-syndrome.html>.

WEBSITES

FriendshipCenter.com. <http://www.friendshipcenter.com>.

NORD—National Organization for Rare Disorders. <http://www.rarediseases.org>.

Suzanne M. Carter, MS, CGC

KEY TERMS

Corpora albicantia—Plural of corpus albicans. A corpus albicans is the scar tissue that remains on an ovarian follicle after ovulation.

Dysgenesis—Defective or abnormal formation of an organ or part usually occuring during embryonic development.

Follicle—A pouch-like depression.

Mosaicism—A genetic condition resulting from a mutation, crossing over, or nondisjunction of chromosomes during cell division, causing a variation in the number of chromosomes in the cells.

Semineferous tubules—Long, threadlike tubes that are packed in areolar tissue in the lobes of the testes.

Spermatozoa—Mature male germ cells that develop in the seminiferous tubules of the testes.

Hermaphroditism

Definition

Hermaphroditism is a rare condition in which ovarian and testicular tissue exist in the same person. The testicular tissue contains seminiferous tubules or spermatozoa. The ovarian tissue contains follicles or corpora albicantia. The condition is the result of a chromosome anomaly.

Description

Among human beings, hermaphroditism is an extremely rare anomaly in which gonads for both sexes are present. External genitalia may show traits of both sexes, and in which the **chromosomes** show male-female mosaicism (where one individual possesses both the male XY and female XX chromosome pairs). There are two different variants of hermaphroditism: true hermaphroditism and pseudohermaphroditism. There are female and male pseudohermaphrodites. True hermaphroditism refers to the presence of both testicular and ovarian tissue in the same individual. The external genitalia in these individuals may range from normal male to normal female. However, most phenotypic males have hypospadias. Pseudohermaphroditism refers to gonadal dysgenesis.

Genetic profile

The most common **karyotype** for a true hermaphrodite is 46XX. **DNA** from the Y chromosome is translocated to one of the X-chromosomes. The karyotype for male pseudohermaphrodites is 46XY. Female pseudohermaphroditism is more complicated. The condition is caused by deficiencies in the activity of enzymes. The genetic basis for three enzyme deficiencies have been identified. Deficiency of 3B hydroxysteroid dehydrogenase—Type 2 is due to an abnormality on chromosome 1p13.1. Deficiency of 21-Hydroxylase is due to an abnormality on chromosome 6p21.3. Deficiency of 11B-Hydroxylase—Type 1 is due to an abnormality on chromosome 8q21.

Demographics

True hermaphrodites are extremely rare. Approximately 500 individuals have been identified in the world to date. Because of the ambiguity of genitalia and difficulties in making an accurate diagnosis, the incidence of pseudohermaphroditism is not well established. The incidence of male pseudohermaphroditism has been estimated at between 3 and 15 per 100,000 people. The incidence of female pseudohermaphroditism has been estimated at between 1 and 8 per 100,000 people.

Signs and symptoms

True hermaphroditism is characterized by ambiguous internal and external genitalia. On internal examination (most often using laparoscopy), there is microscopic evidence of both ovaries and testes. Male pseudohermaphroditism is also characterized by ambiguous internal and external genitalia. However, gonads are often (but not always) recognizable as testes. These are frequently softer than normal. An affected person is often incompletely masculinized. Female pseudohermaphroditism is characterized by female internal genitals. External genitals tend to appear as masculine. This is most commonly characterized by clitoral hypertrophy. Most hermaphrodites are infertile although a small number of pregnancies have been reported.

Diagnosis

True hermaphroditism is often diagnosed after laparoscopic investigation. An initial suspicion of male pseudohermaphroditism is often made by inspection of external genitals. This is confirmed by chromosomal analysis and assays of hormones such as testosterone. Initial suspicion of female pseudohermaphroditism is also made by inspection of external genitals. This is confirmed by analysis of chromosomes and hormonal assay. Laparoscopic examination usually reveals nearly normal female internal genitals.

Treatment and management

Early assignment of gender is important for the emotional well being of any person with ambiguous genitalia. A decision to select a gender of rearing is based on the corrective potential of the ambiguous genitalia, rather than using chromosome analysis. Once the decision is made regarding gender, there should be no question in the family's mind regarding the gender of the child from that point on.

Corrective surgery is used to reconstruct the external genitalia. In general, it is easier to reconstruct female genitalia than male genitalia, and the ease of reconstruction will play a role in selecting the gender of rearing. Treating professionals must be alert for stress in persons with any form of hermaphroditism and their families.

Prognosis

With appropriate corrective surgery, the appearance of external genitalia may appear normal. However, other problems such as virilization may appear later in life. As of 2001, there is some interest among persons with ambiguous genitalia at birth to reverse their gender of rearing.

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ORGANIZATIONS

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937. info@geneticalliance. <http://www.geneticalliance.org>.

Hermaphrodite Education and Listening Post. PO Box 26292, Jacksonville, NY 32226. help@jaxnet.com. <http://users.southeast.net/~help/>.

Intersex Society of North America. PO Box 301, Petaluma, CA 94953-0301. <http://www.isna.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

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Born True Hermaphrodite <http://www.angelfire.com/ca2/BornHermaphrodite/>.

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L. Fleming Fallon, Jr., MD, DrPH

High density hypoprotein deficiency *see* **Tangier disease**

Hirschsprung's disease

Definition

Hirschsprung's disease, also known as congenital megacolon or aganglionic megacolon, is an abnormality in which certain nerve fibers are absent in segments of the bowel, resulting in severe bowel obstruction.

Description

Hirschsprung's disease is caused when certain nerve cells (called parasympathetic ganglion cells) in the wall of the large intestine (colon) do not develop before birth. Without these nerves, the affected segment of the colon lacks the ability to relax and move bowel contents along. This causes a constriction and as a result, the bowel above the constricted area dilates due to stool becoming trapped, producing megacolon (dilation of the colon). The disease can affect varying lengths of bowel segment, most often involving the region around the rectum. In up to 10% of children, however, the entire colon and part of the small intestine are involved.

Genetic profile

Hirschsprung's disease occurs early in fetal development when, for unknown reasons, there is either failure of nerve cell development, failure of nerve cell migration, or arrest in nerve cell development in a segment of bowel. The absence of these nerve fibers, which help control the movement of bowel contents, is what results in intestinal obstruction accompanied by other symptoms.

There is a genetic basis to Hirschsprung's disease, and it is believed that it may be caused by different genetic factors in different subsets of families. Proof that genetic factors contribute to Hirschsprung's disease is that it is known to run in families, and it has been seen in association with some chromosome abnormalities. For example, about 10% of children with the disease have **Down syndrome** (the most common chromosome abnormality). Molecular diagnostic techniques have identified many genes that cause susceptibility to Hirschsprung's disease. As of 200l, there are a total of six genes: the RET gene, the glial cell line-derived neurotrophic factor gene, the endothelin-B receptor gene, endothelin converting enzyme, the endothelin-3 gene, and the Sry-related transcription factor SOX10. Mutations that inactivate the RET gene are the most frequent, occurring in 50% of familial cases (cases which run in families) and 15-20% of sporadic (non-familial) cases. Mutations in these genes do not cause the disease, but they make the chance of developing it more likely. Mutations in other genes or environmental factors are required to develop the disease, and these other factors are not understood.

For persons with a ganglion growth beyond the sigmoid segment of the colon, the **inheritance** pattern is autosomal dominant with reduced penetrance (risk closer to 50%). For persons with smaller segments involved, the inheritance pattern is multifactorial (caused by an interaction of more than one gene and environmental factors, risk lower than 50%) or autosomal recessive (one disease gene inherited from each parent, risk closer to 25%) with low penetrance.

Demographics

Hirschsprung's disease occurs once in every 5,000 live births, and it is about four times more common in males than females. Between 4% and 50% of siblings are also afflicted. The wide range for recurrence is due to the fact that the recurrence risk depends on the gender of the affected individual in the family (i.e., if a female is affected, the recurrence risk is higher) and the length of the aganglionic segment of the colon (i.e., the longer the segment that is affected, the higher the recurrence risk).

Signs and symptoms

The initial symptom is usually severe, continuous constipation. A newborn may fail to pass meconium (the first stool) within 24 hours of birth, may repeatedly vomit yellow or green colored bile and may have a distended (swollen, uncomfortable) abdomen. Occasionally, infants may have only mild or intermittent constipation, often with diarrhea.

While two-thirds of cases are diagnosed in the first three months of life, Hirschsprung's disease may also be diagnosed later in infancy or childhood. Occasionally, even adults are diagnosed with a variation of the disease. In older infants, symptoms and signs may include anorexia (lack of appetite or inability to eat), lack of the urge to move the bowels or empty the rectum on physical examination, distended abdomen, and a mass in the colon that can be felt by the physician during examination. It should be suspected in older children with abnormal bowel habits, especially a history of constipation dating back to infancy and ribbon-like stools.

Occasionally, the presenting symptom may be a severe intestinal infection called enterocolitis, which is life threatening. The symptoms are usually explosive,

watery stools and fever in a very ill-appearing infant. It is important to diagnose the condition before the intestinal obstruction causes an overgrowth of bacteria that evolves into a medical emergency. Enterocolitis can lead to severe diarrhea and massive fluid loss, which can cause death from dehydration unless surgery is done immediately to relieve the obstruction.

Diagnosis

Hirschsprung's disease in the newborn must be distinguished from other causes of intestinal obstruction. The diagnosis is suspected by the child's medical history and physical examination, especially the rectal exam. The diagnosis is confirmed by a barium enema x ray, which shows a picture of the bowel. The x ray will indicate if a segment of bowel is constricted, causing dilation and obstruction. A biopsy of rectal tissue will reveal the absence of the nerve fibers. Adults may also undergo manometry, a balloon study (device used to enlarge the anus for the procedure) of internal anal sphincter pressure and relaxation.

Treatment and management

Hirschsprung's disease is treated surgically. The goal is to remove the diseased, nonfunctioning segment of the bowel and restore bowel function. This is often done in two stages. The first stage relieves the intestinal obstruction by performing a colostomy. This is the creation of an opening in the abdomen (stoma) through which bowel contents can be discharged into a waste bag. When the child's weight, age, or condition is deemed appropriate, surgeons close the stoma, remove the diseased portion of bowel, and perform a "pull-through" procedure, which repairs the colon by connecting functional bowel to the anus. This usually establishes fairly normal bowel function.

Prognosis

Overall, prognosis is very good. Most infants with Hirschsprung's disease achieve good bowel control after surgery, but a small percentage of children may have lingering problems with soilage or constipation. These infants are also at higher risk for an overgrowth of bacteria in the intestines, including subsequent episodes of enterocolitis, and should be closely followed by a physician. Mortality from enterocolitis or surgical complications in infancy is 20%.

Prevention

Hirschsprung's disease is a congenital abnormality that has no known means of prevention. It is important to diagnose the condition early in order to prevent the development of enterocolitis. **Genetic counseling** can be offered to a couple with a previous child with the disease or to an affected individual considering pregnancy to discuss recurrence risks and treatment options. Prenatal diagnosis is not available.

KEY TERMS

Anus—The opening at the end of the intestine that carries waste out of the body.

Barium enema x ray—A procedure that involves the administration of barium into the intestines by a tube inserted into the rectum. Barium is a chalky substance that enhances the visualization of the gastrointestinal tract on x-ray.

Colostomy—The creation of an artificial opening into the colon through the skin for the purpose of removing bodily waste. Colostomies are usually required because key portions of the intestine have been removed.

Enterocolitis—Severe inflammation of the intestines that affects the intestinal lining, muscle, nerves and blood vessels.

Manometry—A balloon study of internal anal sphincter pressure and relaxation.

Meconium—The first waste products to be discharged from the body in a newborn infant, usually greenish in color and consisting of mucus, bile and so forth.

Megacolon—Dilation of the colon.

Parasympathetic ganglion cell—Type of nerve cell normally found in the wall of the colon.

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ORGANIZATIONS

American Pseudo-Obstruction & Hirschsprung's Society. 158 Pleasant St., North Andover, MA 01845. (978) 685-4477.

Pull-thru Network. 316 Thomas St., Bessemer, AL 35020. (205) 428-5953.

Amy Vance MS, CGC

HLA region *see* **Major histocompatibility complex**

Holoprosencephaly

Definition

Holoprosencephaly is a disorder in which there is a failure of the front part of the brain to properly separate into what is commonly know as the right and left halves of the brain. This lack of separation is often accompanied by abnormalities of the face and skull. Holoprosencephaly may occur individually or as a component of a larger disorder.

Description

Types of holoprosencephaly

Holoprosencephaly comes in three different types: alobar, semilobar, and lobar. Each of these classifications is based on the amount of separation between what is commonly known as the left and right halves of the brain. Alobar holoprosencephaly is considered to be the most severe form of the disease, in which the separation between the two halves, or hemispheres, completely fails to develop. Semilobar holoprosencephaly represents holoprosencephaly of the moderate type, where some separation between the hemispheres has occurred. Lobar holoprosencephaly represents the least severe type of holoprosencephaly in which the hemispheres are almost, but not completely, divided.

The severity of the effect of the disease on the brain is often reflected in craniofacial abnormalities (abnormalities of the face and skull). This has led to many health care professionals utilizing the phrase "the face predicts the brain." This phrase is generally but not always accurate. Children may have severe craniofacial abnormalities with mild (lobar) holoprosencephaly, or children may have severe (alobar) holoprosencephaly with mild facial changes. Since the development of the face, skull, and the front of the brain are interconnected, the changes in the face often, but do not always, correspond with changes in the brain. Finally, the designation of these disorders from least severe to most severe can be mildly misleading, since the best predictor of the severity of the disease, according to Barr and Cohen, is how well the brain functions, not its appearance. However, the alobar, semilobar, and lobar categories are universally utilized and give an indication of the severity of the disease, so knowledge of these categories and what they represent is useful.

Other brain abnormalities in holoprosencephaly

All patients with holoprosencephaly lack a sense of smell through the first cranial nerve (the olfactory nerve). Interestingly enough, one has a partial sense of smell through the sense of taste, which is governed by the seventh cranial nerve. The term "smell" and what it means in a conventional and strictly neurological sense differ, so it may be useful to think of persons with holoprosencephaly as lacking a portion of what is in common usage referred to as smell. This deficiency in smell can be detected by testing. One other important structural abnormality should be mentioned. The corpus callosum, which is the part of the brain that connects the right and left hemispheres with each other, is absent or deficient in persons with holoprosencephaly.

Synonyms for holoprosencephaly

Arrhinencephaly and familial alobar holoprosencephaly are synonyms for this disorder.

Genetic profile

Genetic causes of holoprosencephaly

Holoprosencephaly is a feature frequently found in many different syndromes including, but not limited to: trisomy 13, **trisomy 18**, tripoloidy, pseudotrisomy 13, **Smith-Lemli-Opitz syndrome**, **Pallister-Hall syndrome**, **Fryns syndrome**, **CHARGE association**, **Goldenhar syndrome**, frontonasal **dysplasia**, **Meckel-Gruber syndrome**, velocardiofacial syndrome, Genoa syndrome, Lambotte syndrome, Martin syndrome, and Steinfeld syndrome, as well as several teratogenic syndromes such as diabetic embryopathy, **accutane embryopathy**, and **fetal alcohol syndrome**. Holoprosencephaly has been linked to at least 12 different loci on 11 different **chromosomes**. Some candidate genes are Sonic hedge-

hog (abbreviated Shh, and located at 7q36), SIX3 (located at 2p21), and the ZIC2 gene (located on chromosome 13). The gene causing Smith-Lemli-Opitz syndrome, which affects cholesterol synthesis, also is interesting, since it is also obviously a candidate to cause holoprosencephaly.

Shh, cholesterol, the prechordal plate, and the cause of holoprosencephaly

Holoprosencephaly probably arises in one of two ways (suggested by experiments in animal models). Early in the life of an embryo, an area called the prechordal plate forms. The prechordal plate is an area of the embryo which is important for the formation of the brain. The prechordal plate is said to induce brain formation. One can think of the induction process in the following way. If you take a sponge, wet it, and then place a paper towel on top of it, the paper towel will absorb some of the water. In the same way, a signal (the water) goes from the sponge (prechordal plate) to the paper towel (future brain tissue). If the water doesn't hit the paper towel, brain tissue will not form. This is an extremely simplified version of how the process works, for many reasons. One is that the prechordal plate is not the only "sponge." The notochord is another sponge, which sends out the signal (water) of Shh to form brain and spinal cord and other nervous tissue. Of course, Shh has already been mentioned as a candidate for a gene which causes holoprosencephaly. It turns out it is better than a candidate, because mutations in Shh have been found in some familial forms of holoprosencephaly. Further evidence that Shh plays a role in holoprosencephaly comes from Shh in mice and fish, which both result in holoprosencephaly. Thus, it would be a nice, clear-cut picture if mutations in Shh and Shh alone led to holoprosencephaly, because Shh mutations lead to holoprosencephaly in other animals and Shh is already known to be involved in the formation of neural tissue.

However, Shh is not the only answer. Many persons with holoprosencephaly have perfectly normal Shh genes, and, as previously mentioned, a number of genes have been linked to holoprosencephaly, including genes involved in cholesterol synthesis. So why are so many genes involved?

One possible answer stems from the connection between cholesterol and the Shh signaling pathway. When Shh travels from one tissue to another tissue, there are a number of other genes involved before Shh has its final effect. This process is called signal transduction, and the genes that make it up are part of a signaling pathway. Signal transduction can be compared to a shot in the game of pool. When shooting pool, one must take the cue (Shh), hit the cue ball (another gene; for Shh this would be the gene Patched), and the cue ball goes on to hit the ball that one is interested in sinking (in this case sinking the ball means making a normal brain). Thus, each step depends on the last step and the next step. If one doesn't have the stick or the cue ball one cannot sink the ball in the pocket. Thus, a number of mutations in genes in the Shh signaling pathway, and not just Shh, could cause holoprosencephaly. Not just that, but other genes involved in cholesterol biosynthesis can have effects on genes in the Shh signaling pathway. Cholesterol appears to affect the function of the gene Patched. In the pool example, a lack of cholesterol would not mean the cue ball is gone, but maybe that the cue ball has a big lump on one side, so the shot is likely to miss.

Another possible answer comes from studies on bone morphogenetic proteins (BMPs) in chickens. Up until now, the problem of holoprosencephaly has been addressed as if it occurs when neural tissue is formed. However, the presence of too much BMP in a chick embryo after the time neural tissue is formed can cause holoprosencephaly. It appears there are two stages that can be interfered with: one that occurs at the time of neural tissue formation involving Shh, and another that occurs later involving BMPs. Increased levels of BMPs may cause important neural cells to die. It has been speculated that holoprosencephaly is either a failure to grow neural cells due to failure in Shh pathway, or an excess of neural cells dying possibly due to increased levels of BMPs. Both may end up being true, with some Shh signaling defects early, and BMP mutations later.

Teratogens also cause holoprosencephaly

A **teratogen** is any environmental influence that adversely affects the normal development of the fetus. Teratogens can be skin creams, drugs, or alcohol. Alcohol, when ingested in sufficient amounts during the second week of pregnancy, is thought to lead to some

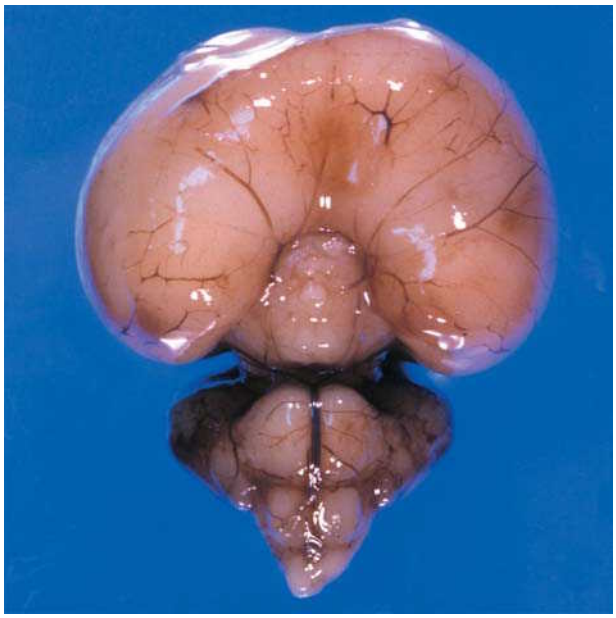
KEY TERMS

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Craniofacial—Relating to or involving both the head and the face.

Induction—Process where one tissue (the prechordal plate, for example) changes another tissue (for example, changes tissue into neural tissue).

Neural—Regarding any tissue with nerves, including the brain, the spinal cord, and other nerves.



The most severe form of holoprosencephaly, alobar holoprosencephaly, results when the brain fails to separate into the right and left lobes. *(Greenwood Genetic Center)*

cases of holoprosencephaly. Cytomegalovirus infections in the mother during pregnancy have also been associated with holoprosencephaly. Additionally, in animals, drugs inhibiting cholesterol synthesis have been shown to cause cases of holoprosencephaly. Finally, the drug cyclopamine, which affects the Shh pathway, also causes holoprosencephaly in animals. Cyclopamine was discovered when an abnormally large number of sheep were found to have holoprosencephaly. A local shepherd and scientists determined the drug was found in a fungus called Veratrum californicum.

Demographics

Holoprosencephaly affects males and females at the same rate. Estimates vary on the frequency of the disorder in children with normal chromosomes. The estimates range from one case in every 11,363 births to one case in 53,394 births. It is important to note that this rate of incidence excludes those cases which are caused by **chromosomal abnormalities**, like trisomy 13.

Signs and symptoms

In holoprosencephaly alone, symptoms involve the brain and/or the face and bones of the face and skull. Facial abnormalities exhibit a wide range. In the most severe cases, persons with holoprosencephaly lack eyes and may lack a nose. Less severe is cyclopia, or the presence of a single eye in the middle of the face above the possibly deformed or absent nose. Even less severe are ethmocephaly and cebocephaly, in which the eyes are set close together and the nose is abnormal. In premaxillary agenesis the patient has a midline cleft lip and cleft palate and close-set eyes. If the face is very abnormal, the patient is likely to have alobar holoprosencephaly, the most severe type. In addition to abnormalities of the face, children with alobar holoprosencephaly also have small brains (less than 100g). These children also have small heads unless they have excess cerebrospinal fluid. Excess cerebrospinal fluid can cause the head to be abnormally large.

Persons with holoprosencephaly experience many problems due to brain malformations including in utero or neonatal death. Survivors may experience seizures, problems with muscle control and muscle tone, a delay in growth, problems feeding (choking and gagging or slowness, pauses, and a lack of interest), intestinal gas, constipation, hormone deficiencies from the pituitary, breathing irregularities, and heart rhythm and heart rate abnormalities. These problems are usually least severe in lobar holoprosencephaly and most severe in alobar. Children with holoprosencephaly also experience severe deficiencies in their ability to speak and in their motor skills. An ominous sign that children with holoprosencephaly may exhibit is a sustained (lasting many hours or days) period of irregular breathing and heart rate. This may precede death. However, episodes lasting only minutes are usually followed by a full recovery.

Diagnosis

Prenatal ultrasound and computerized tomography can be used to determine whether the fetus has holoprosencephaly and its severity. After birth, physical appearance and/or imaging of the brain can determine a diagnosis of holoprosencephaly. Once a diagnosis of holoprosencephaly has been made, syndromes of which holoprosencephaly is a part must be considered. Forty-one percent of holoprosencephaly cases are thought to have a chromosomal abnormality as the primary cause. Holoprosencephaly is estimated to be found in the context of a larger syndrome in 25% of the remaining cases.

Treatment and management

Although no treatment exists for the underlying disease, symptomatic treatment can reduce the amount of fluid surrounding the brain and assist in feeding. Medical intervention can reduce or eliminate seizures and hormonal deficiencies. However, few treatments exist for the most serious aspects of the disease—breathing and heart arrhythmias (irregular heart rate)—or for the problems associated with developmental delay and poor muscle control. One important aspect of treatment is to help parents understand the effects of the disease and what may

be expected from the child. Support groups, like the one listed at the end of this entry, may be important for this purpose. Parents should also be prepared to deal with a large number of health care professionals based on their child's particular needs.

Prognosis

About half of the children born with alobar holoprosencephaly die before the age of four to five months, but a much longer survival time is possible, up to at least 11 years. Children with semilobar and lobar holoprosencephaly may live for any length of time. Depending on the severity of the holoprosencephaly, however, parents should be prepared for differences in their child. For example, children with alobar holoprosencephaly and semilobar holoprosencephaly learn to speak very little, if at all, and children with alobar holoprosencephaly have difficulty even mastering the simple task of reaching and grasping an object. On the other end of the spectrum, children may develop much more normally. It is very important to understand the severity of the disorder to understand the child's abilities and possibilities.

Resources

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Michael V. Zuck, PhD

Holt-Oram syndrome

Definition

Holt-Oram syndrome (HOS) is one of several hereditary conditions characterized by abnormalities of the heart and hands at birth.

Description

HOS involves variable abnormalities of the heart and the hands, or hands and arms. The heart abnormalities may range from disturbances in the electrical conduction pattern of the heart to severe structural defects requiring surgical intervention for survival. The abnormalities of the upper limbs are usually bilateral (occurring on both sides) and asymmetric (not identical from side to side). The severity of the upper limb changes may range from minor signs, such as clinodactyly (inward curvature of the fingers) to disabling defects, such as small or missing bones resulting in very short arms.

Some individuals with HOS are so mildly affected, they do not require any special care or treatment. Other individuals are severely affected and may have significant disability resulting from abnormalities of the arms, or may have limited lifespans due to serious heart abnormalities. The signs of HOS are usually limited to the heart and skeleton. HOS does not cause mental retardation.

Some references may use the alternative name of hand-heart syndrome. However, Holt-Oram syndrome is one of many hereditary hand-heart syndromes, so the two names are not truly interchangeable.

Genetic profile

HOS is inherited as an autosomal dominant condition, with variable expressivity (meaning that different individuals with HOS may have very different signs of the condition) and complete penetrance (meaning that every individual that has the genetic change causing the condition has some physical symptoms). An autosomal dominant condition only requires the presence of one abnormal **gene** on a non-sex-linked chromosome for the disorder to occur. Some researchers have observed families with incomplete penetrance (meaning that not every individual with the gene abnormality shows symptoms) as well.

In some individuals and families, HOS is caused by mutations in the TBX5 gene located on the long arm of chromosome 12. The TBX5 gene encodes a transcription factor that helps regulate **DNA** expression. Other families with HOS do not show mutations in the TBX5 gene, indicating that mutations in other genes can also cause HOS. HOS families that have TBX5 mutations do not appear to differ significantly from those which do not.

Some patients with HOS have inherited it from an affected parent, whereas others have it as the result of a new change in a gene. The proportion of patients with HOS resulting from new mutations ranges from 8% to 85%. Regardless of where the gene came from, an affected individual has a 50% chance of passing on the gene and the condition to each child. It is difficult to predetermine the severity of symptoms a child may have.

Demographics

Since HOS was first described in 1960, more than 200 cases have been reported in individuals of diverse ethnicity. The incidence of the condition has been estimated as 1/100,000 live births.

Signs and symptoms

All individuals with HOS have some degree of upper limb abnormality, and most (approximately 95% in familial cases) have defects or dysfunction of the heart. Other body parts and systems are usually not significantly affected by HOS.

Defects of the upper limbs

The limb abnormalities in HOS primarily affect the radial side (the inner or thumb side of the arm/hand). Involvement of the ulnar side (the outer side of the arm/hand, opposite the thumb) may also occur to a lesser degree. In some individuals, the abnormality of the upper limb may be very mild, such as hypoplasia (underdevelopment) of the muscle at the base of the thumb, limited rotation of the arm, or narrow, sloping shoulders. Rarely, severe abnormalities of the upper limbs may be present, resulting in extremely short, "flipper-like" arms. Abnormalities of the upper limb are always bilateral and usually asymmetric. In 90% of patients, the left side is more severely affected.

The thumb is the most commonly affected part of the upper limb in HOS, and is affected in some way in 84% of patients. Some individuals have three phalanges (or bones) in the thumb, resulting in a thumb that can bend in three places, like a finger. In other cases, the thumb may be hypoplastic (underdeveloped). Syndactyly (or skin webbing) may occur between the thumb and index finger.

Abnormalities of the fingers may include hypoplasia, underdevelopment, or absence of one or more fingers. Clinodactyly (inward curvature) of the fifth or "pinky" finger is also common. In some patients, polydactyly (extra fingers) has been reported.

The bones of the arms may also be affected by HOS. The radius (the inner bone of the forearm, adjacent to the thumb) may be hypoplastic or even missing. Such patients may have a lesser degree of hypoplasia of the ulna (outer bone of the forearm, opposite the thumb). The upper arm may be short. In rare cases, as noted above, the bones of the arm are dramatically shortened, resulting in a tiny arm.

Individuals with HOS often appear to have narrow, sloping shoulders. This likely results from some degree of hypoplasia of the clavicles (collarbones), as well as decreased musculature which occurs secondarily to bone hypoplasia.

Defects and dysfunction of the heart

The vast majority (95%) of individuals with HOS who have inherited it from an affected parent have heart involvement. Most have a defect in the structure of the heart. In some patients, there is no structural defect in the heart, but abnormalities are present in the pattern of electrical conduction in the heart.

The most common heart abnormalities in people with HOS are septal defects, or holes in the heart. A hole may occur in the wall separating the atria of the heart (atrioseptal defect or ASD), or the wall separating the ventricles of the heart (ventriculoseptal defect or VSD). In rare cases, more severe and complex heart defects may occur, such as hypoplastic left heart (in which the chambers of the left side of the heart are too small to function normally) or tetralogy of fallot (a specific combination of four heart defects). In the case of severe defects, surgical correction is necessary for survival. However, most persons with HOS do not require surgical intervention.

Some individuals with HOS have a cardiac conduction defect, or an abnormal electrical pattern in the heart. The complex motion of the heart requires a system of electrical impulses for coordinated contraction of the muscle fibers. In people with cardiac conduction defects, these electrical impulses may not occur in the normal pattern, resulting in an abnormal heartbeat. In rare cases, this can result in sudden death.

Other defects

Additional skeletal abnormalities occasionally reported in patients with HOS include **scoliosis**, vertebral abnormalities, and minor deformities of the rib cage. Some patients may have abnormalities unrelated to the cardiac or skeletal systems, such as minor eye defects and various birthmarks. It is not clear whether these additional findings are coincidental or part of HOS.

Diagnosis

The diagnosis of HOS is made on the basis of the clinical judgment by a specialist physician, usually a geneticist, following physical examination and review of pertinent tests or studies. Diagnostic criteria may be employed to guide this decision. One commonly used set of criteria for the diagnosis of HOS require that there be 1) defect(s) of the radial side of the hand/arm, as well as 2) septal defect(s) or conduction abnormality of the heart, within one individual or family.

X rays may be necessary to determine involvement of the bones of the upper limb. Diagnosis of structural

defects of the heart requires echocardiography, or ultrasound visualization of the heart. Conduction defects of the heart are identified via electrocardiography (EKG). This test involves measuring the electrical activity of the heart and charting the electrical impulses associated with each heartbeat.

Testing to identify changes in the TBX5 gene may be offered, but is not necessary for a diagnosis of HOS. Identification of a change or alteration in the TBX5 gene could provide confirmation of the clinical diagnosis, prenatal diagnosis, or assist in the diagnosis of at-risk family members who are minimally affected. Prenatal screening in a pregnancy at risk for HOS may also be attempted by fetal ultrasonography targeted toward the fetal arms and heart. However, a normal ultrasound examination does not eliminate the possibility of HOS in the unborn baby.

Treatment and management

There is no specific treatment for HOS. Surgery or other treatment may be recommended for cardiac abnormalities. Referral for **genetic counseling** should be considered for families in which HOS has been diagnosed.

Some patients with HOS have life-threatening heart defects that require surgical correction for survival. The most complex heart defects may require multiple surgeries. However, many individuals have asymptomatic or no heart abnormalities. When life-threatening irregularities are present in the heartbeat, a pacemaker device is inserted. These devices correct the abnormal electrical patterns which cause the irregularities and stimulate the heart to beat normally.

Because eye abnormalities have been occasionally reported in HOS, an eye examination may be recommended at the time of diagnosis.

Prognosis

The prognosis for individuals with HOS depends on the severity of associated birth defects, which varies considerably. Positive correlation has been reported between the severity of upper limb and heart defects. In other words, individuals who have more severe hand or arm involvement may be more likely to have a symptomatic heart defect. People who have HOS resulting from new mutations are more likely to have severe defects than those who have inherited it from a parent.

In some cases, HOS may lead to death in early infancy due to multiple septal defects or other complex structural abnormalities of the heart. Severe and unrecognized disturbances of the cardiac conduction system can lead to sudden death. In other cases, heart involvement is limited to asymptomatic irregular heartbeat requiring no treatment.

KEY TERMS

Atria—The two chambers at the top of the heart, where blood from the lungs or body pools before entering one of the ventricles.

Polydactyly—The presence of extra fingers or toes.

Radius—One of the two bones of the forearm, the one adjacent to the base of the thumb.

Septal defect—A hole in the heart.

Syndactyly—Abnormal webbing of the skin between the fingers or toes.

Ulna—One of the two bones of the forearm, the one opposite the thumb.

Ventricles—One of the chambers (small cavities) of the heart through which blood circulates. The heart is divided into the right and left ventricles.

Several unusual findings have been described with respect to the severity of HOS in families. Affected women have been reported to have a higher chance of having a severely affected child than do affected men. The severity of defects associated with HOS has also been reported to increase with successive generations. The possible explanations for these observations are not known.

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Jennifer A. Roggenbuck, MS, CGC

Homocystinuria

Definition

The term homocystinuria is actually a description of a biochemical abnormality, as opposed to the name of a particular disease, although many refer to homocystinuria as a disease. Homocystinuria refers to elevated levels of homocysteine in the urine. This can be caused by different biochemical abnormalities and in fact there are

KEY TERMS

Anabolism—The energy-using process of building up complex chemical compounds from simpler ones in the body.

Catabolism—The energy-releasing process of breaking down complex chemical compounds into simpler ones in the body.

Marfan syndrome—A syndrome characterized by skeletal changes (arachnodactyly, long limbs, lax joints), ectopia lentis, and vascular defects.

Thrombophilia—A disorder in which there is a greater tendency for thrombosis (clot in blood vessel).

at least eight different **gene** changes that are known to cause excretion of too much homocysteine in the urine. The best known and most common cause of homocystinuria is the lack of cystathionine b-synthase. For the purpose of this entry we will be referring to "classical homocystinuria" that is caused by cystathionine b-synthase deficiency (CBS deficiency).

Description

In Northern Ireland in the early 1960s, homocystinuria was described in individuals who were mentally retarded. Soon after that, it was shown that the cause of the homocystinuria was a deficiency of the enzyme cystathionine b-synthase. This condition is an inborn error of metabolism, meaning that the cause for this condition is present from birth and it affects metabolism.

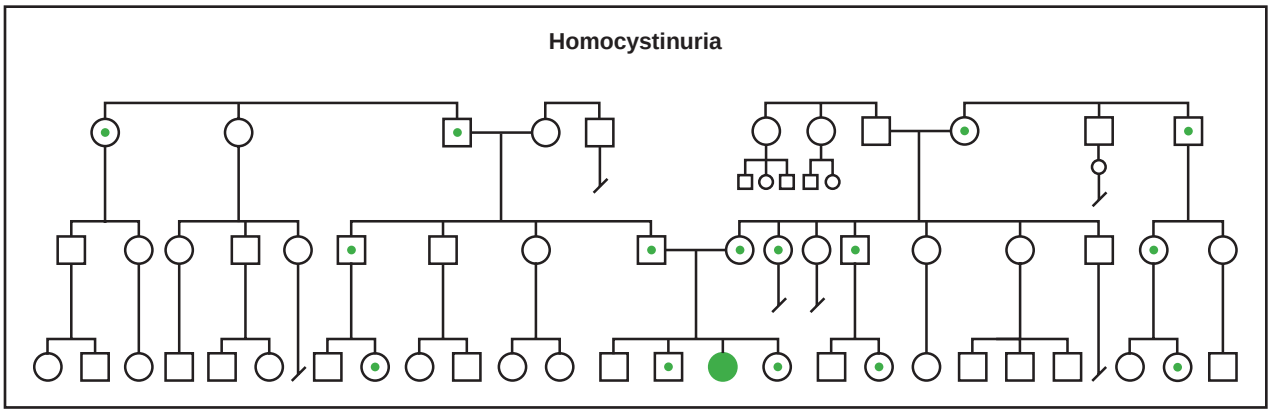
Metabolism is the sum of all of the chemical processes that take place in the body. Metabolism includes both construction (anabolism) and break down (catabolism) of important components. For example, amino acids are the building blocks for proteins and are converted to proteins through many steps in the process of anabolism. In contrast, proteins can also be broken down into amino acids through many steps in the process of catabolism. These processes require multiple steps that involve different substances called enzymes. These enzymes are proteins that temporarily combine with reactants and in the process, allow these chemical processes to occur quickly. Since practically all of the reactions in the body use enzymes, they are essential for life. At any point along the way, if an enzyme is missing, the particular process that requires that enzyme would not be able to be completed as usual. Such a situation can lead to disease.

Homocysteine is involved with the catabolism of methionine. Methionine is an essential amino acid. Amino acids are the building blocks of proteins. Over 100 amino acids are found in nature, but only 22 are found in humans. Of these 22 amino acids, eight are essential for human life, including methionine. Methionine comes from dietary protein. Generally, the amount of methionine that is consumed is more than the body needs. Excess methionine is converted to homocysteine, which is then metabolized into cystathionine; cystathionine is then converted to cysteine. The cysteine is excreted in the urine. Each step along this pathway is carried out by a specific enzyme and that enzyme may even require help from vitamin co-factors to be able to complete the job. For example, the conversion of homocysteine to cystathionine by cystathionine b-synthase requires vitamin B_6 (pyridoxine). If cystathionine b-synthase is missing, then homocysteine cannot be broken down into cystathionine and cysteine, and instead, homocysteine accumulates and the elevated levels of homocysteine and methionine can be found in the blood. Also, decreased levels of cysteine can be found in the blood. Elevated levels of homocysteine lead to a disease state that, if untreated, affects multiple systems, including the central nervous system, the eyes, the skeleton, and the vascular system.

Genetic profile

Classical homocystinuria or cystathionine b-synthase (CBS) deficiency is an autosomal recessive condition. This means that in order to have the condition, an individual must inherit one copy of the gene for CBS deficiency from each parent. An individual who has only one copy of the gene is called a carrier for the condition. In most cases of autosomal recessive **inheritance** a carrier for a condition does not have any signs, symptoms, or effects of the condition. This is not necessarily the case with CBS deficiency. Individuals who are carriers for CBS deficiency may have levels of homocysteine that are elevated enough to increase the risk for thromboembolic events. So, although carriers may not exhibit obvious physical signs or symptoms of the condition, they may have clinical effects of elevated levels of homocysteine, such as vascular or cardiovascular disease. A carrier for CBS deficiency can have vascular complications, especially if they are also carriers for other clotting disorders such as **factor V Leiden thrombophilia**.

When two parents are carriers for CBS deficiency, there is a one in four or 25% chance, with each pregnancy, for having a child with CBS deficiency. They have a one in two or 50% chance for having a child who is a carrier for the condition and a one in four or 25% chance for having a child who is neither affected nor a carrier for CBS deficiency.



(Gale Group)

The gene for CBS has been mapped to the long arm of chromosome 21, specifically at 21q22.3. Approximately 100 different disease-associated gene changes or alterations of the CBS gene have been identified. The two most frequently encountered gene changes are 1278T and G307S. G307S is the most common cause of CBS deficiency in Irish patients and the 1278T gene is the most common cause of CBS deficiency in Italian patients.

Demographics

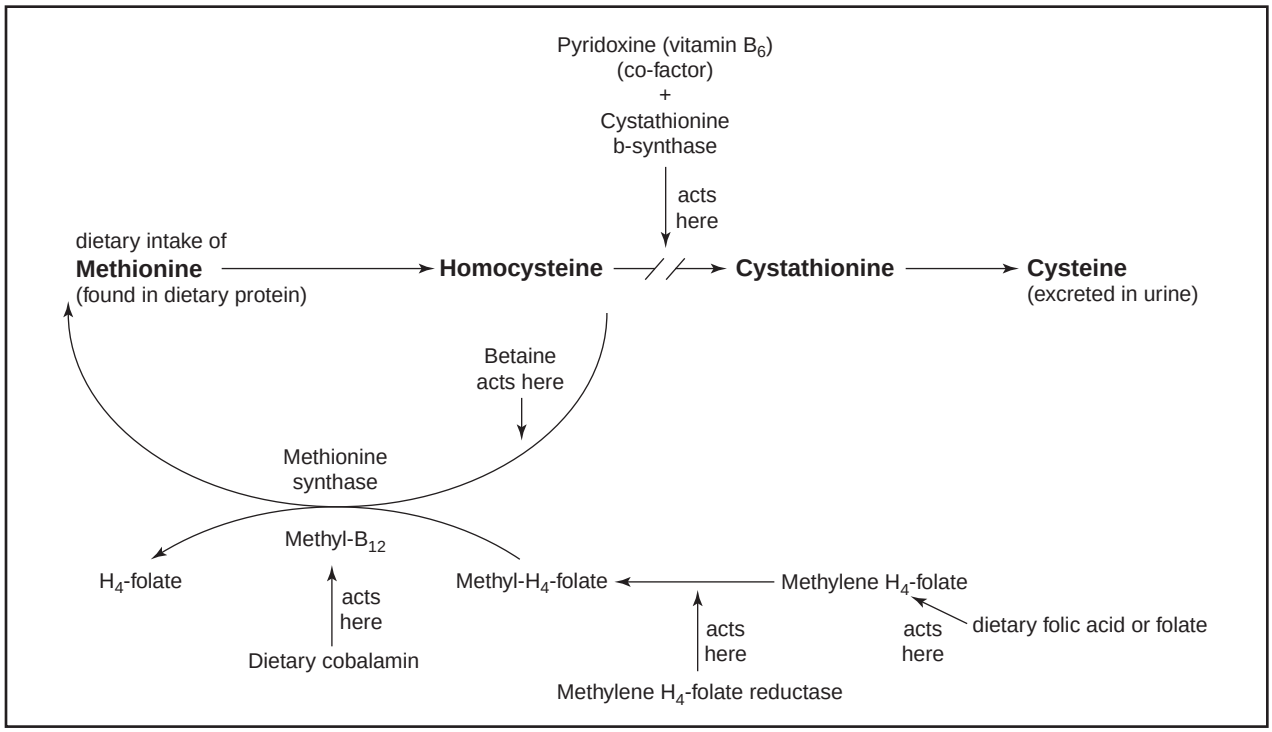
The worldwide frequency of individuals with CBS deficiency who are identified through newborn screening and clinical detection is approximately one in 350,000; however, newborn screening may be missing half of affected patients and thus the worldwide incidence may be as high as one in 180,000. One study showed that by lowering the cutoff level of methionine from 2 mg per deciliter to 1 mg per deciliter in newborn screening, detection of the deficiency increased from 1 in 275,000 to 1 in 157,000. The incidence of CBS deficiency in the United States population is 1 in 58,000; in the Irish population it is estimated to be 1 in 65,000; in the Italian population it is 1 in 55,000 and in the Japanese population it is 1 in 889,000. CBS deficiency has been seen in persons of many different ethnic origins living in the United States.

Signs and symptoms

Individuals who have CBS deficiency tend to be tall and thin with thinning and lengthening of the bones. They tend to have a long, narrow face and high arched palate (roof of the mouth). The thinning and lengthening of the long bones causes individuals to be tall and thin by the time they reach late childhood. Their fingers tend to be long and thin as well (referred to as arachnodactyly). They can have curvature of the spine, called **scoliosis**. Their chest can be sunken in (pectus excavatum) or it may protrude out (pectus carinatum). Osteoporosis may occur. Also, they tend to have stiff joints. CBS deficiency affects the eyes, causing dislocated lenses and nearsightedness (**myopia**). Untreated individuals or those individuals who do not respond to treatment develop mental retardation or learning disabilities. Affected individuals may also develop psychiatric problems. These psychiatric problems may include **depression**, chronic behavior problems, chronic obsessive-compulsive disorder, and personality disorders. The most frequent cause of death associated with CBS deficiency is blood clots that form in veins and arteries. These are known as thromboembolisms, and include deep vein thrombosis (blood clots that form in the deep veins of the legs, etc.), pulmonary embolus (blood clots that form in the lungs), and strokes. Thromboembolism can occur even in childhood. When thromboembolism does occur in childhood, CBS deficiency should always be considered as a cause for the thromboembolic events. These thromboembolic events can occur in any part of the body. Lastly, another complication of CBS deficiency is severe premature arteriosclerosis (hardening of the arteries).

Diagnosis

Approximately 50% of individuals who have CBS deficiency are diagnosed by newborn screening because they have an elevated level of methionine in their blood. The reason for performing newborn screening is so that infants affected with **genetic disorders** can be identified early enough to be treated. The screening is done by collecting blood from a pin-prick on the baby's heel prior to leaving the hospital, but at least 24 hours after birth. For CBS deficiency, the screening test checks for elevated levels of methionine. If the levels are elevated then follow-up testing to verify the diagnosis is performed. There are other disorders of methionine metabolism, and follow-up testing determines the underlying cause of the positive newborn screen.



Flow chart for the chemical processes involved in the breakdown of methionine, an essential amino acid found in dietary protien. Homocystinuria results when the enzyme cystathionine b-synthase is missing and does not break down homocystine, a converted form of excess methionine. The elevated levels of methionine and homocystein that result from the failure of homocysteine to break down into cystathionine and cysteine causes a disease state that affects multiple body systems. *(Gale Group)*

If not identified at newborn screening, diagnosis is made by identifying low levels of cysteine in blood and urine. Measurements of the amount of methionine and homocysteine produced by cultured blood cells (lymphoblasts) or cultured skin cells (fibroblasts) also can confirm the diagnosis of CBS deficiency.

DNA testing is available for families in which a gene alteration is identified. Potentially, this makes prenatal diagnosis by chorionic villus sampling (CVS) and **amniocentesis** available for families who have had a previously affected child and in which two identifiable gene alterations for CBS deficiency have been detected. Prenatal diagnosis is also possible by measuring the amount of enzyme activity in cultured cells grown from amniotic fluid.

CBS deficiency has several features in common with **Marfan syndrome**, including the tall, thin build with long limbs and long, thin fingers (arachnodactyly), a sunken-in chest (pectus excavatum), and dislocated lenses. The dislocated lens in Marfan syndrome tends to be dislocated upward; the tendency for the lens dislocation is to be downward in CBS deficiency. Also, individuals who have Marfan syndrome tend to have lens dislocation from birth (congenital) whereas individuals who have CBS deficiency have not been identified to have lens dislocation before 2 years of age.

Treatment and management

The first choice of therapy for patients with CBS deficiency is administration of pyridoxine (vitamin B_6). Vitamin B_6 is the cofactor for the cystathionine b-synthase reaction. Potentially, some individuals who have CBS deficiency are not missing the enzyme, but rather have an enzyme that is unable to perform its job. The addition of pyridoxine can help to push the reaction along and thus help to reduce the levels of homocysteine and methionine in the blood. Information suggests that approximately 50% of patients with CBS deficiency respond to high doses of pyridoxine (pyridoxine responsive) and show a significant reduction in levels of homocysteine in the blood. Patients who do not respond to pyridoxine treatment (pyridoxine non-responsive) tend to be more severely affected than the patients who do respond. Those non-responding patients are treated with combinations of folic acid, hydroxycobalamin, and betaine, which stimulate the conversion of homocysteine back to methionine. The reason that the addition of folic acid can help is because within the methylene H4-folate

(MTHFR) molecule, there is a molecule known as flavin adenine dinucleotide, or FAD. The FAD molecule binds to the MTHFR molecule and helps with the conversion of homocysteine to methionine. Increased levels of folates help bind FAD more tightly to MTHFR, protect the enzyme against heat inactivation, and allow the homocysteine to methionine conversion pathway to proceed. Betaine and cobalamin also help in the conversion of homocysteine to methionine by acting as cofactors. The rationale behind this method of treatment is that although the methionine levels are raised, the net drop in homocysteine is beneficial as it appears that the elevated levels of homocysteine are what cause ectopia lentis, osteoporosis, mental deficiency, and thromboembolic events.

It appears that the addition of dietary betaine in B_6-responsive patients is also beneficial. Homocysteine that is not metabolized to cysteine is converted back to methionine in a reaction that uses betaine, so the addition of betaine may help to make this reaction occur and thus reduce the levels of homocysteine.

Other treatments include protein restriction, specifically a low methionine diet with the addition of extra cysteine. Dietary treatment includes avoidance of all high protein foods throughout life, with the use of a nutritional supplement. Special formulas for infants are available. The reasoning behind this is to reduce the methionine and homocysteine levels that accumulate and supplement the low levels of cysteine.

The occurrence of clinically apparent thromboembolism depends upon the age of the affected individual and whether or not he/she responds to pyridoxine treatment. In one study, untreated pyridoxine-responsive patients were at little risk for a thromboembolic event until age 12. After age 12, the risk for thromboembolism increased. By age 20, patients who would have been responsive to pyridoxine had a 25% cumulative risk for a thromboembolic event. In comparison, individuals with CBS deficiency who were untreated and not responsive to pyridoxine treatment had a similar cumulative risk for a thromboembolic event by age 15.

In reference to the two common CBS gene alterations, CBS deficiency caused by the 1278T gene change is pyridoxine responsive. CBS deficiency caused by the G307S gene tends to be pyridoxine non-responsive; however this is not always the case as some individuals with the G307S gene change are pyridoxine responsive.

Very little is known about the risks to an unborn child of a mother with pyridoxine non-responsive CBS deficiency. There have been numerous reports of healthy children born to women and men who have pyridoxine responsive CBS deficiency, however only two reports of children born to pyridoxine non-responsive women have been reported and one had multiple birth defects that may have been related to the mother's condition. Potentially, the mother's elevated levels of homocysteine can cause problems for a developing baby. This could be similar to the process by which infants of mothers who have phenylketonuria are affected by the elevated levels of phenylalanine if their mothers are not being treated with dietary restriction during pregnancy.

Prognosis

Untreated CBS deficiency leads to mental retardation, lens dislocation, and a decreased life expectancy because of complications associated with blood clots. If untreated from early infancy, approximately 20% of affected patients will have seizures. If treated from birth, prevention or long term delay of the complications of CBS deficiency can be expected.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

Climb: Children Living with Inherited Metabolic Diseases Support Group. <http://www.climb.org.uk>.

Reneé A. Laux, MS

Homogentisic acid oxidose deficiency *see* Alkaptonuria

Human Genome Project

The Human Genome Project (HGP) is the international project to sequence the **DNA** of the human genome. The sequencing work is conducted in many laboratories around the world, but the majority of the work is being done by five institutions: the Whitehead Institute for Medical Research in Massachusetts (WIMR), the Baylor College of Medicine in Texas, the University of Washington, the Joint Genome Institute in California, and the Sanger Centre near Cambridge in the United Kingdom. Most of the funding for these centers is provided by the United States National Institute of Health and Department

of Energy, and the Wellcome Trust, a charitable foundation in the UK.

Completely sequencing the human genome was first suggested at a conference in Alta, Utah in 1984. The conference was convened by the U.S. Department of Energy, which was concerned with measuring the mutation rate of human DNA when exposed to low-level radiation, similar to conditions after an attack by nuclear weapons. The technology to make such measurements did not exist at the time, and the sequence of the genome was one step required for this aim to become possible. The genome was estimated to be 3000Mb long, however, and sequencing it seemed an arduous task, especially using the sequencing technology of the time. If most of the DNA was "junk" (not coding for genes), then scientists assumed that they could speed the process along by targeting specific genes for sequencing. This could be done by sequencing complementary DNAs (cDNA) which are derived from mRNAs used to code for proteins in the cell. Despite several advocates for this method, it was decided that the whole genome would be sequenced, with a target completion date of 2005. The Human Genome Project quickly became the world's premier science project for biology, involving large factory-like laboratories rather than small laboratories of independent geneticists.

The strategy employed by the HGP involved three stages, and is termed hierarchical shotgun sequencing. The first stage involved generating physical and genetic maps of the human genome. The second stage was placing clones from a genomic library on to these maps. The third stage was fragmenting these genomic clones into smaller overlapping clones (shotgun cloning), which were a more suitable size for sequencing. Then, the complete sequence of each chromosome could be reconstructed by assembling the fragments of sequence that overlapped with each other to generate the sequence of the genomic clone. The sequence of each genomic clone could then be fitted together using the assembly (contig) of genomic clones on the genetic and physical map.

Although the ultimate aim was high-quality sequence of the human genome, it was recognized that the genetic and physical maps generated by the first stage of the HGP would be by themselves very useful for genetic research. The first generation physical map was constructed by screening a yeast artificial chromosome (YAC) genomic library to isolate YACs, and overlaps were identified by restriction enzyme digest "fingerprints" and STS content mapping. These STSs were sequenced around the highly polymorphic CA-repeat markers (microsatellites) that were used to generate the genetic map. Genetic maps were also constructed. These use recombination between markers in families to deduce the distance separating and order of these markers. The first human genetic map used restriction fragment length polymorphisms (RFLPs) as markers, which only have two alleles per marker, but common microsatellites were used to create a high resolution genetic map.

The second stage of human genome sequencing was made simpler by the development of bacterial artificial **chromosomes** (BACs), cloning vectors that could carry up to 150kb of DNA. Before then, it was assumed that a contig of YACs and cosmids, carrying up to 2Mb and 40kb of DNA respectively, would be assembled. These two types of genomic clone were found to be liable to rearrangement; the DNA in the vector could be in chunks that were not necessarily in the same order as in the genome. The BAC vector did not rearrange DNA, and could carry more DNA than many other types of genomic clone.

The third stage was made easier by development of high-throughput DNA sequencing and affordable computing power to enable reassembly of the sequence fragments. It was these developments that led to the idea of whole genome shotgun sequencing of the human genome. In contrast to the HGP plan involving the use of genetic contigs and physical maps as a framework for genomic clones and sequence, scientists suggested that the whole genome could be fragmented into small chunks for sequencing, and then reassembled using overlap between fragment sequences (whole genome shotgun sequencing). This required large amounts of computing power to generate the correct assembly, but was considerably faster than the HGP approach. Many scientists did not believe that this method would assemble the genome properly, and suggested that overlap between small fragments could not be the only guide to assembly, because the genome contained many repeated DNA sequences. However, American biochemist J. Craig Venter believed the method could work, and formed Celera, a private company that would sequence the human genome before the HGP. Celera demonstrated that the whole genome shotgun method would work by sequencing the genome of a model organism, the fruit fly *Drosophila melanogaster*. Despite the successful sequencing of the fly, many people were still skeptical that the method would be successful for the bigger human genome. The publicly funded HGP, in light of Celera's competition, decided to concentrate, like Celera, on a draft of the human genome sequence (3x coverage—that is each nucleotide has been sequenced an average of three times), before generating a more accurate map of 8x coverage. Celera had an advantage, because the HGP had agreed to release all its data as it was generated on to a freely accessible database, as part of the Bermuda rules (named after the location of a series of meetings during the early stages of the HGP). This allowed Celera to use

HGP data to link its sequence fragments with the BAC contigs and genetic/physical maps.

The human genome draft sequence of both groups were published in February 2001 by Celera and the HGP consortium in the journals *Science* and *Nature*, respectively. Celera had imposed restrictions on access to its genomic data, and this was a source of disagreement between the private company and the HGP. Celera scientists argue that their methods are cheaper and quicker than the HGP framework method, but HGP scientists, in turn, argue that Celera's assembly would not have been possible without the HGP data.

For human geneticists in general, and medical researchers in particular, the genome sequence is abundantly useful. Even in its draft form (the complete version is due in 2003) the ability to identify genes, single nucleotide polymorphisms, from a database search speeds up research. Previously, mapping and finding (positional cloning) a **gene** would take several years of research, a task which now takes several minutes. The investment in the sequencing centers will continue to be of use, with a mouse sequencing project underway, and many genomes of pathogenic bacteria sequenced. This study of genomes and parts of genomes has been called genomics. The medical benefits of genomics were emphasized throughout the project partly to ensure continuing government support. These benefits are not likely to be immediate nor direct, but the genome sequence will have the greatest effect on pharmocogenetics, which studies how genetic variants can affect how well a drug can treat a disease. The impact on non-scientists has been substantial, with the HGP suggested to be the ultimate in self knowledge. Although the mapping of the human genome by the HGP is an important scientific achievement, WIMR director Eric Lander offered a humbling perspective regarding the amount of information yet to be discovered by future generations of scientists. In a speech at the White House, Lander said, "We've called the human genome the blueprint, the Holy Grail, all sorts of things. It's a parts list. If I gave you the parts list for the Boeing 777, and it has 100,000 parts, I don't think you could screw it together, and you certainly wouldn't understand why it flew."

Edward J. Hollox, PhD

Hunter syndrome

Definition

Hunter syndrome is a defect in the ability to metabolize a type of molecule known as a mucopolysaccharide. Only males are affected. Short stature, changes in the normal curvature of the spine (kyphosis), a distinctive facial appearance characterized by coarse features, an oversized head, thickened lips, and a broad, flat nose characterize the syndrome.

KEY TERMS

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Mucopolysaccharide—A complex molecule made of smaller sugar molecules strung together to form a chain. Found in mucous secretions and intercellular spaces.

Description

Hunter syndrome is a one of a group of diseases called mucopolysaccharidoses. It is caused by the deficiency of an enzyme that is required to metabolize or break down mucopolysaccharides (also called glycosaminoglycans). It is also called mucopolysaccharidosis Type II (MPS II) because there are several related but similar diseases. The Hunter syndrome involves a defect in the extracellular matrix of connective tissue. One of the components of the extracellular matrix is a molecule called a proteoglycan. Like most molecules in the body, it is regularly replaced. When this occurs, one of the products is a class of molecules known as mucopolysaccharides (glycosoaminoglycans). Two of these are important in Hunter syndrome: dermatan sulfate and heparan sulfate. These are found in the skin, blood vessels, heart and heart valves (dermatan sulfate) and lungs, arteries and cellular surfaces (heparan sulfate). The partially broken-down molecules are collected by lysosomes and stored in various locations in the body. Over time, these accumulations of partially metabolized mucopolysaccharides impair the heart, nervous system, connective tissue, and bones.

Both of these molecules require the enzyme iduronate-2-sulfatase (I2S) to be broken down. In people with Hunter syndrome, this enzyme is partially or completely inactive. As a result, unchanged molecules accumulate in cells. These mucopolysaccharides are stored and interfere with normal cellular functions. The rate of accumulation is not the same for all persons with Hunter syndrome. Variability in the age of onset is thought to be due to lingering amounts of activity by this enzyme.

The cells in which mucopolysaccharides are stored determine the symptoms that develop. When mucopolysaccharides are stored in skin, the proportions of the face change (coarser features than normal and an enlarged

head). When they are stored in heart valves and walls, cardiac function progressively declines. If intact mucopolysaccharides are stored in airways of the lung, difficulty in breathing develops due to obstruction of the upper airway. Storage of the molecules in joints decreases mobility and dexterity. Storage in bones results in decreased growth and short stature. As mucopolysaccharides are stored in the brain, levels of mental functioning decline.

There are two variants of Hunter syndrome: a severe form (MPSIIA) and a mild form (MPSIIB). These can be diagnosed early in life and are distinguished on the basis of mental and behavioral differences. External manifestations of the severe form occur between two and four years of age and the mild form later, up to age 10.

Genetic profile

In both variants, the missing enzyme is L-Sulfoiduronate. Hunter syndrome is X-linked meaning that the I2S **gene** is located on the X chromosome. The Y chromosome of a male is never affected in Hunter syndrome. Males only have one copy of the I2S gene while females have two. A male who inherits an abnormal I2S gene will develop Hunter syndrome. This can occur in two ways: from a mother who already has the gene (she is a carrier) or from a fresh mutation. Fresh mutations are unusual.

There are four possible genetic configurations. (1) A male can have a normal I2S gene and will be unaffected. (2) A male can have an abnormal I2S gene and will have Hunter syndrome. Should this male reproduce, his sons will not have Hunter syndrome and his daughters will all be carriers. (3) A female can have two normal I2S genes and be unaffected. (4) A female can have one abnormal I2S gene and be a carrier. Should this female reproduce, half of her sons will, on average, have Hunter syndrome. Half of her daughters, on average, will be carriers. It is possible that no sons will have Hunter syndrome or no daughters will be carriers.

Demographics

Several estimates of the incidence of Hunter syndrome have been published. They vary from one in 72,000 male births (Northern Ireland) to one in 150,000 (United States). Because it is carried on the X chromosome, only males can be affected.

Signs and symptoms

Individuals with Hunter syndrome experience a slowing of growth between one and four years of age. They attain an average height of 4-5 feet (122-152 cm). The facial features of persons with Hunter syndrome are coarser than normal. Their heads tend to be large in proportion to their bodies. Over time, their hands tend to become stiff and assume a claw-like appearance. Their teeth are delayed in erupting. Progressive hearing loss eventually leads to deafness. Internal organs such as the liver and spleen are larger than normal. They are quite prone to hernias.

Diagnosis

Hunter syndrome can be identified early in life and is often initially diagnosed by the presence of an enlarged liver and spleen (hepatosplenomegaly), hernias, or joint stiffness. Skeletal changes can be seen with radiographs. Elevated mucopolysaccharide levels in urine focuses the diagnosis to a group of disorders. The concentration of dermatan sulfate and heparan sulfate is 5-25 times higher than in normal urine. Both are present in approximately the same amounts. The diagnosis of Hunter syndrome is confirmed by measuring iduronate-2-sulfatase activity in white blood cells, serum, or skin fibroblasts. Prenatal diagnosis is widely available by measuring the activity of I2S enzyme in amniotic fluid.

Hunter syndrome has many diagnostic characteristics in common with **Hurler syndrome**. However, there are some distinct differences between the two syndromes. Individuals with Hunter syndrome have clear corneas and tend to have deposits of mucopolysaccharides in the skin. These are characteristically on the back of the hands and elbows (the extensor surfaces) and on the upper surfaces of the shoulders. All are males. These differences are important in diagnosis.

Treatment and management

General support and treatment of specific symptoms are the only treatment options presently available. Iduronate-2-sulfatase can be made using cells that have been genetically engineered. However, as of 2001, the safety and clinical effectiveness of injecting I2S into humans has not been established.

Intrauterine testing of amniotic fluid is reliable. Tests to detect a carrier state are imperfect. There is no cure for Hunter syndrome. The heparan sulfate and dermatan sulfate in urine has no pathological significance.

Prognosis

In the severe form, death usually occurs by age 10-15. Persons with the mild form usually live near-normal lives and have normal intelligence.

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Canadian Society for Mucopolysaccharide and Related Diseases. PO Box 64714, Unionville, ONT L3R-OM9 Canada. (905) 479-8701 or (800) 667-1846. <http://www.mpssociety.ca>.

Children Living with Inherited Metabolic Diseases. The Quadrangle, Crewe Hall, Weston Rd., Crewe, Cheshire, CW1-6UR UK. 127 025 0221. Fax: 0870-7700-327. <http://www.climb.org.uk>.

National MPS Society. 102 Aspen Dr., Downingtown, PA 19335. (601) 942-0100. Fax: (610) 942-7188. info@mpssociety.org. <http://www.mpssociety.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Society for Mucopolysaccharide Diseases. 46 Woodside Rd., Amersham, Buckinghamshire, HP6 6AJ UK. +44 (01494) 434156. <http://www.mpssociety.co.uk>.

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L. Fleming Fallon, Jr., MD, DrPH

Huntington chorea *see* **Huntington disease**

Huntington disease

Definition

Huntington disease is a progressive, neurodegenerative disease causing uncontrolled physical movements and mental deterioration. The disease was discovered by George Huntington of Pomeroy, Ohio, who first described a hereditary movement disorder.

Description

Huntington disease is also called Huntington chorea, from the Greek word for "dance," referring to the involuntary movements that develop as the disease progresses. It is occasionally referred to as "Woody Guthrie disease" for the American folk singer who died from it. Huntington disease (HD) causes progressive loss of cells in areas of the brain responsible for some aspects of movement control and mental abilities. A person with HD gradually develops abnormal movements and changes in cognition (thinking), behavior, and personality.

Demographics

The onset of symptoms of HD is usually between the ages of 30 and 50, although in 10% of cases, onset is in late childhood or early adolescence. Approximately 30,000 people in the United States are affected by HD, with another 150,000 at risk for developing this disorder. The frequency of HD is four to seven per 100,000 persons.

Genetic profile

Huntington disease is caused by a change in the **gene** (an inherited unit which contains a code for a protein) of unknown function called huntingtin. The nucleotide codes (building blocks of genes arranged in a specific code that chemically form proteins), contain CAG repeats (40 or more of these repeat sequences). The extra building blocks in the huntingtin gene cause the protein that is made from it to contain an extra section as well. It is currently thought that this extra protein section, or portion, interacts with other proteins in brain cells where it occurs, and that this interaction ultimately leads to cell death.

The HD gene is a dominant gene, meaning that only one copy of it is needed to develop the disease. HD affects both males and females. The gene may be inherited from either parent, who will also be affected by the disease. A parent with the HD gene has a 50% chance of passing it on to each offspring. The chances of passing on the HD gene are not affected by the results of previous pregnancies.

KEY TERMS

Cognition—The mental activities associated with thinking, learning, and memory.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Heimlich maneuver—An action designed to expel an obstructing piece of food from the throat. It is performed by placing the fist on the abdomen, underneath the breastbone, grasping the fist with the other hand (from behind), and thrusting it inward and upward.

Neurodegenerative—Relating to degeneration of nerve tissues.

Signs and symptoms

The symptoms of HD fall into three categories: motor or movement symptoms, personality and behavioral changes, and cognitive decline. The severity and rate of progression of each type of symptom can vary from person to person.

Early motor symptoms include restlessness, twitching and a desire to move about. Handwriting may become less controlled, and coordination may decline. Later symptoms include:

- Dystonia, or sustained abnormal postures, including facial grimaces, a twisted neck, or an arched back.
- Chorea, in which involuntary jerking, twisting, or writhing motions become pronounced.
- Slowness of voluntary movements, inability to regulate the speed or force of movements, inability to initiate movement, and slowed reactions.
- Difficulty speaking and swallowing due to involvement of the throat muscles.
- Localized or generalized weakness and impaired balance ability.
- Rigidity, especially in late-stage disease.

Personality and behavioral changes include **depression**, irritability, anxiety and apathy. The person with HD may become impulsive, aggressive, or socially withdrawn.

Cognitive changes include loss of ability to plan and execute routine tasks, slowed thought, and impaired or inappropriate judgment. Short-term memory loss usually occurs, although long-term memory is usually not affected. The person with late-stage HD usually retains knowledge of his environment and recognizes family members or other loved ones, despite severe cognitive decline.

Diagnosis

Diagnosis of HD begins with a detailed medical history, and a thorough physical and neurological exam. Family medical history is very important. Magnetic resonance imaging (MRI) or computed tomography scan (CT scan) imaging may be performed to look for degeneration in the basal ganglia and cortex, the brain regions most affected in HD.

A genetic test is available for confirmation of the clinical diagnosis. In this test, a small blood sample is taken, and **DNA** from it is analyzed to determine the CAG repeat number. A person with a repeat number of 30 or below will not develop HD. A person with a repeat number between 35 and 40 may not develop the disease within their normal lifespan. A person with a very high number of repeats (70 or above) is likely to develop the juvenile-onset form. An important part of **genetic testing** is extensive **genetic counseling**.

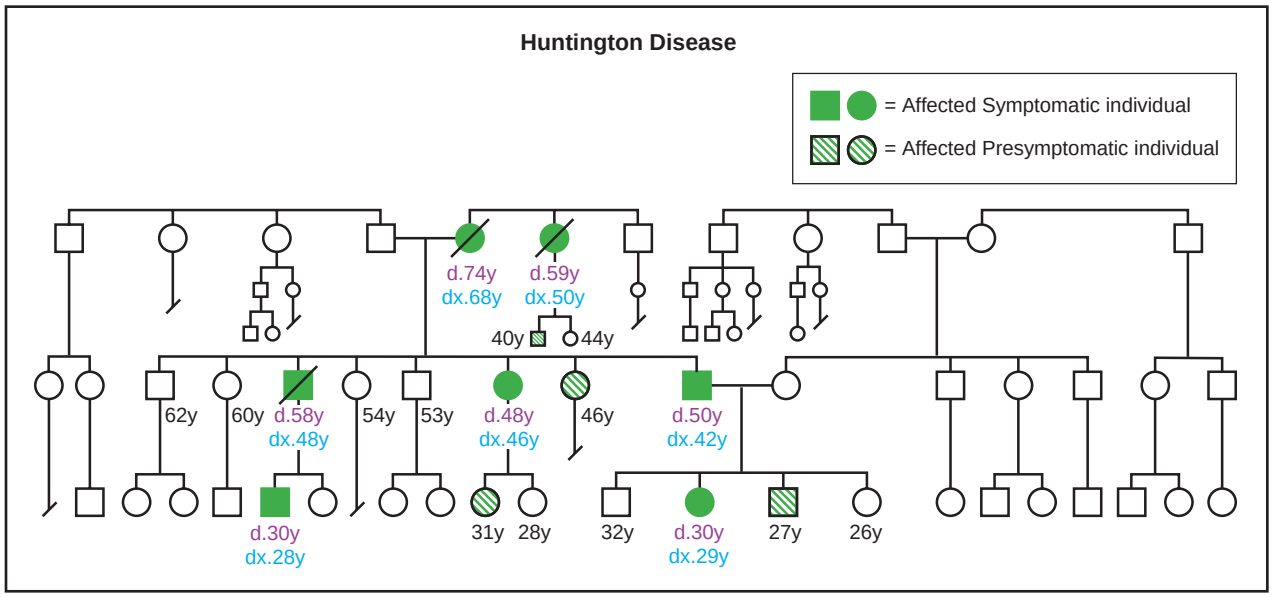
Prenatal testing is available. A person at risk for HD (a child of an affected person) may obtain fetal testing without determining whether she herself carries the gene. This test, also called a linkage test, examines the pattern of DNA near the gene in both parent and fetus, but does not analyze for the triple nucleotide repeat (CAG). If the DNA patterns do not match, the fetus can be assumed not to have inherited the HD gene, even if present in the parent. A pattern match indicates the fetus probably has the same genetic makeup of the at-risk parent.

Treatment and management

There is no cure for HD, nor any treatment that can slow the rate of progression. Treatment is aimed at reducing the disability caused by the motor impairments, and treating behavioral and emotional symptoms.

Physical therapy is used to maintain strength and compensate for lost strength and balance. Stretching and range of motion exercises help minimize contracture, or muscle shortening, a result of weakness and disuse. The physical therapist also advises on the use of mobility aids such as walkers or wheelchairs.

Motor symptoms may be treated with drugs, although some studies suggest that anti-chorea treatment rarely improves function. Chorea (movements caused by abnormal muscle contractions) can be suppressed with



(Gale Group)

drugs that deplete dopamine, an important brain chemical regulating movement. As HD progresses, natural dopamine levels fall, leading to loss of chorea and an increase in rigidity and movement slowness. Treatment with L-dopa (which resupplies dopamine) may be of some value. Frequent reassessment of the effectiveness and appropriateness of any drug therapy is necessary.

Occupational therapy is used to design compensatory strategies for lost abilities in the activities of daily living, such as eating, dressing, and grooming. The occupational therapist advises on modifications to the home that improve safety, accessibility, and comfort.

Difficulty swallowing may be lessened by preparation of softer foods, blending food in an electric blender, and taking care to eat slowly and carefully. Use of a straw for all liquids can help. The potential for choking on food is a concern, especially late in the disease progression. Caregivers should learn the use of the Heimlich maneuver. In addition, passage of food into the airways increases the risk for pneumonia. A gastric feeding tube may be needed, if swallowing becomes too difficult or dangerous.

Speech difficulties may be partially compensated by using picture boards or other augmentative communication devices. Loss of cognitive ability affects both speech production and understanding. A speech-language pathologist can work with the family to develop simplified and more directed communication strategies, including speaking slowly, using simple words, and repeating sentences exactly.

Early behavioral changes, including depression and anxiety, may respond to drug therapy. Maintaining a calm, familiar, and secure environment is useful as the disease progresses. Support groups for both patients and caregivers form an important part of treatment.

Experimental transplant of fetal brain tissue has been attempted in a few HD patients. Early results show some promise, but further trials are needed to establish the effectiveness of this treatment.

Prognosis

The person with Huntington disease may be able to maintain a job for several years after diagnosis, despite the increase in disability. Loss of cognitive functions and increase in motor and behavioral symptoms eventually prevent the person with HD from continuing employment. Ultimately, severe motor symptoms prevent mobility. Death usually occurs 15–20 years after disease onset. Progressive weakness of respiratory and swallowing muscles leads to increased risk of respiratory infection and choking, the most common causes of death. Future research in this area is currently focusing on nerve cell transplantation.

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ORGANIZATION

Huntington Disease Society of America. 140 W. 22nd St. New York, NY 10011. (800) 345-HDSA.

Laith F. Gulli, MD

Hurler syndrome

Definition

Hurler syndrome is a disorder that results when cells cannot break down two by-products of normal metabolism. These byproducts, dermatan sulfate and heparan sulfate, build up and disrupt normal cell function, leading to severe disease. The disease affects most body systems, causing progressive deterioration of tissues and organs.

Description

Though present from conception, Hurler syndrome may be undetectable at birth. The newborn often looks healthy and seems to develop normally for the first few months. However, symptoms begin to appear around the age of six months, when dermatan sulfate and heparan sulfate reach dangerous levels.

Individuals with Hurler syndrome lack sufficient amounts of the enzyme needed to break down dermatan sulfate and heparan sulfate. This enzyme, alpha-L-iduronidase, is part of a biochemical pathway which splits complex molecules into smaller, recyclable units. Without alpha-L-iduronidase, the complex molecules cannot be eliminated and deposit themselves in cells, tissues, and organs. Deposits in the soft tissues of the face lead to a typical appearance, causing children with Hurler syndrome to resemble each other more than they resemble their own healthy siblings. The spleen and liver become enlarged early in the course of the disease. Deposits stored in the growth plates of bones lead to dwarfism, **scoliosis**, joint stiffness, and other skeletal abnormalities. Corneal clouding caused by the deposits results in vision damage. Hearing loss usually occurs as well. Deposits in the brain cause loss of skills gained early in life, and severe mental retardation occurs.

The accumulation of dermatan sulfate and heparan sulfate in the airways leads to frequent respiratory tract and ear infections. Deposits also cause coronary artery obstruction and damage to the heart. In fact, respiratory complications and heart failure are the most frequent causes of death in Hurler syndrome patients. Many children with Hurler syndrome die by the age of 12.

Dermatan sulfate and heparan sulfate belong to a class of complex molecules known as mucopolysaccharides, chains formed by smaller sugar molecules strung together. For this reason, Hurler syndrome is also known as a mucopolysaccharidosis, a name meaning, “too many mucopolysaccharides.” To be precise, Hurler syndrome is called Mucopolysaccharidosis I H (MPS I H). There are several other mucopolysaccharidoses, each resulting from absence or deficiency of a different enzyme.

Sometimes Hurler syndrome is called a lysosomal storage disease. Lysosomes are cell parts which normally contain enzymes needed to break down complex molecules. When the enzymes are absent or deficient, the lysosomes store the complex molecules, expand, and eventually destroy the cells from within.

Hurler syndrome takes its most commonly used name from Gertrud Hurler, the German pediatrician who first described the condition in her patients.

Genetic profile

Researchers have identified the **gene** responsible for Hurler syndrome and have mapped it to the 4p16.3 site on chromosome 4. The gene is named IDUA, for the iduronidase enzyme which it produces when working properly. As of 2001, researchers have connected 52 different IDUA mutations to cases of Hurler syndrome.

Hurler syndrome is an autosomal recessive disorder. This means that it occurs only when a person inherits two defective copies of the IDUA gene. If one copy is normal and the other has a mutation, the person does not have Hurler syndrome. However, the person carries the mutated gene and can pass it on to the next generation.

Carriers of IDUA mutations have only one working gene. As a result, these carriers produce less alpha-L-iduronidase enzyme than do people with two normal IDUA genes. Nevertheless, they produce enough enzyme to break down dermatan sulfate and heparan sulfate, so disease does not occur.

Demographics

Hurler syndrome affects males and females of all races and ethnic groups. It is a rare disorder, occurring in about one out of 100,000 people.

Different IDUA gene mutations appear more frequently in certain populations. For instance, two specific mutations account for most Hurler syndrome cases among Northern Europeans, while two other mutations appear most often in Japanese patients.

Signs and symptoms

A child with Hurler syndrome may be born with a hernia. In fact, hernia is often the first sign of this disorder. However, since it can also occur in other conditions or as an isolated event, it does not immediately point to Hurler syndrome.

Other symptoms appear within six to twelve months of birth. Tissue damage in airways leads to breathing difficulties and frequent respiratory and ear infections. The child’s face begins to take on the coarse, typical features

of Hurler syndrome. The skull appears large and unusually shaped, scalp veins are prominent, and the bridge of the nose is flat. The lips are large and the mouth is frequently open due to an enlarged, protruding tongue. Teeth may be late to emerge and are usually small, short, widely spaced, and somewhat malformed. The earlobes are thick, and the eyelids are full.

Skeletal abnormalities begin to appear. The hands are broad, with short, stubby fingers. Joints are often stiff and may limit the child's movement. The neck is very short; the spine is crooked and bends outward, resulting in a hunchback appearance.

Children under the age of one may already show signs of heart disease. This is usually due to tissue damage in the arteries or valves of the heart, caused by accumulation of dermatan sulfate and heparan sulfate. Accumulation also causes the liver and spleen to become severely enlarged, but these organs continue to function normally.

Hurler syndrome has a devastating effect on mental development. By the age of one or two, developmental delay occurs. The child may make slow progress for a few more years, but then actually begins to lose skills gained earlier. The mental capacity of a person with Hurler syndrome is similar to that of a normal three-year-old. Deterioration of the senses makes this situation worse. Corneal clouding damages vision. Hearing loss, narrowed airways, and enlarged tongue contribute to poor language skills.

Many infants with Hurler syndrome grow quickly during their first few months. However, skeletal abnormalities and progressive tissue damage cause growth to slow down and then to stop before it should. As a result, most people with Hurler syndrome do not grow beyond four feet tall.

Diagnosis

Hurler syndrome shares many symptoms with other mucopolysaccharidoses and with different lysosomal storage diseases. For this reason, laboratory tests are used to confirm Hurler syndrome diagnosis based on a physical exam.

The simplest test available is urine screening. People with Hurler syndrome excrete increased amounts of dermatan sulfate and heparan sulfate in their urine. In addition, a blood test reveals deficiency of alpha-L-iduronidase enzyme. White blood cells and skin cells can be microscopically examined for damage caused by deposits of dermatan sulfate and heparan sulfate.

If Hurler syndrome is present in a family, healthy family members could carry a mutated IDUA gene.

KEY TERMS

Alpha-L-iduronidase—An enzyme that breaks down dermatan sulfate and heparan sulfate. People with Hurler syndrome do not make enough of this enzyme.

Hernia—A rupture in the wall of a body cavity, through which an organ may protrude.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mucopolysaccharide—A complex molecule made of smaller sugar molecules strung together to form a chain. Found in mucous secretions and intercellular spaces.

Mucopolysaccharidosis I H (MPS I H)—Another name for Hurler syndrome.

Tracheostomy—An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

Several clinical laboratories offer carrier screening to these individuals. A blood sample is all that is required. Most labs screen for carrier status by measuring the level of the alpha-L-iduronidase enzyme. Levels are lower in carriers than they are in people who have two normal IDUA genes. It is also possible to examine the actual genes to see if a Hurler syndrome mutation appears.

Since Hurler syndrome is a rare disorder, most carriers have children with non-carrier partners. Thus there is generally no risk of the disease occurring in the children. However, if two carriers have children together, each child has a 25% chance of having Hurler syndrome. Carrier screening provides an opportunity to assess the risk and consider reproductive options before pregnancy occurs.

Each child born to two carriers has a 50% risk of inheriting one mutated gene and one normal gene. This child, like the parents, is a carrier.

Because a rare autosomal recessive gene can be passed for generations before two carriers have a child together, sometimes an affected child is born into a family with no previous history of Hurler syndrome. This is generally an indication that both parents carry a mutated IDUA gene. These parents worry not only about the health of the affected child, but also about the risk to future children.

Prenatal testing is available to find out if a fetus has Hurler syndrome. This can be done by **amniocentesis** or chorionic villus sampling. Amniocentesis involves removal of a small amount of amniotic fluid from the uterus. Chorionic villus sampling involves removal of a small sample of placental tissue. In either case, the cells present in the sample are checked for enzyme deficiency or gene mutations.

Treatment and management

Treatment of individual Hurler syndrome symptoms does not cure the disease, but it does offer some relief. Surgical repair is available to correct a hernia. Hearing aids sometimes improve hearing and language skills, and eyeglasses may enhance eyesight. Some children with Hurler syndrome improve communication skills by learning sign language.

Skeletal abnormalities require attention, especially if they affect the upper part of the spine and compress the spinal cord. Spinal cord compression and storage of dermatan sulfate and heparan sulfate in the surrounding membranes cause fluid to accumulate in the brain. Brain damage often occurs unless this condition is corrected. A surgeon can implant a shunt in the brain to remove excess fluid. Once present, the mental retardation caused by Hurler syndrome is generally not reversible.

It is important to protect the upper back and neck of a patient with Hurler syndrome. This area should not be manipulated during chiropractic or physical therapy. If the patient undergoes anesthesia for any reason, care should be taken to support the neck and upper back at all times.

Orthopedic treatment can help reduce joint stiffness and its effects on movement.

Several options are available to correct breathing difficulties. Some patients respond well to oxygen treatments. Others require tonsillectomy, adenoidectomy or tracheostomy to remove upper airway obstruction. Medications are available to treat common respiratory infections.

If heart disease is limited to valve damage, valve replacement may be an option for some patients with Hurler syndrome.

Children with Hurler syndrome are generally easygoing and affectionate. They benefit greatly from safe and caring environments. Community support and social services can improve the quality of life for the entire family unit. The family of a child with Hurler syndrome experiences grief and loss throughout the lifetime and upon the death of the child. **Genetic counseling** is available to offer support, educate families about the disease, and assess the risk to other family members. The National MPS Society provides additional support and information.

As of 2001, bone marrow transplant (BMT) is the only treatment that appears to improve the long-term outcome of children with Hurler syndrome. BMT replaces the child's entire blood system with the blood system of a healthy person. The healthy bone marrow contains stem cells, cells from which other cells and tissues arise. These cells produce enough alpha-L-iduronidase to break down dermatan sulfate and heparan sulfate.

Bone marrow transplant is a complicated procedure. If the donated bone marrow is not compatible with the child's own body tissues, the child's immune system will destroy it. BMT is most successful if the donor is a close relative of the patient, since this increases the chance of compatibility between donor and patient bone marrow. To reduce the risk of donor bone marrow rejection, the patient receives drugs and radiation to suppress the immune system, leaving the patient vulnerable to infection.

Research indicates that children with Hurler syndrome do better if BMT takes place before the age of two. Beyond that point, prevention or correction of brain damage is unlikely, and other body tissues may be so severely affected that the child would not survive BMT.

Prognosis

As of 2001, bone marrow transplant is the only treatment that can prevent or reduce the effects of Hurler syndrome. However, bone marrow transplant is not an option for every patient. Some patients with severe disease are too weak to survive the transplant procedure or recovery period. For some, a donor match is not available. Others don't have access to the technological or medical expertise needed for the procedure. In addition, some patients who have bone marrow transplants reject the donor cells.

Research into long-term therapies is underway. Two which appear promising are enzyme replacement therapy and **gene therapy**.

Enzyme replacement involves giving the patient a substitute for the deficient enzyme. The patient would receive regular enzyme injections, similar to insulin injections used by people with diabetes. Enzyme replacement is complicated in a disorder which affects many different tissues, as Hurler syndrome does. Each tissue interacts differently with the enzyme. For this reason, it is difficult to design a substitute which works with various tissues. Furthermore, the brain has a natural barrier against outside substances. This is called the blood-brain barrier, and it stops the enzyme substitute from reaching

brain cells. Therefore, an enzyme substitute injected into the blood would not prevent or reduce the brain damage caused by Hurler syndrome. The substitute might, however, reduce damage to other tissues of the body.

Gene therapy attempts to introduce a normal gene into the patient's cells. In theory, the cells would then incorporate the gene, copy it, and produce enough enzyme to break down complex molecules.

Until these or other therapies become available, patients who cannot undergo BMT can receive treatment for individual Hurler syndrome symptoms. While treatment provides temporary relief, it cannot prevent the progressive damage caused by accumulation of dermatan sulfate and heparan sulfate. Death due to respiratory complications or heart failure usually occurs by age 12.

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ORGANIZATIONS

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937 info@geneticalliance. <http://www.geneticalliance.org>.

National MPS Society. 102 Aspen Dr., Downingtown, PA 19335. (610) 942-0100. Fax: (610) 942-7188. info @mpssociety.org. <http://www.mpssociety.org>.

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Avis L. Gibons

Hutchinson-Gilford progeria syndrome *see* **Progeria**

Hydrocephalus

Definition

Hydrocephalus is an abnormal expansion of cavities (ventricles) within the brain that is caused by the accumulation of cerebrospinal fluid. Hydrocephalus comes from two Greek words: *hydros* means water and *cephalus* means head.

There are two main varieties of hydrocephalus: congenital and acquired. An obstruction of the cerebral aqueduct (aqueductal stenosis) is the most frequent cause of congenital hydrocephalus. Acquired hydrocephalus may result from **spina bifida**, intraventricular hemorrhage, meningitis, head trauma, tumors, and cysts.

Description

Hydrocephalus is the result of an imbalance between the formation and drainage of cerebrospinal fluid (CSF). Approximately 500 milliliters (about a pint) of CSF is formed within the brain each day, by epidermal cells in structures collectively called the choroid plexus. These cells line chambers called ventricles that are located within the brain. There are four ventricles in a human brain. Once formed, CSF usually circulates among all the ventricles before it is absorbed and returned to the circulatory system. The normal adult volume of circulating CSF is 150 ml. The CSF turnover rate is more than three times per day. Because production is independent of absorption, reduced absorption causes CSF to accumulate within the ventricles.

There are three different types of hydrocephalus. In the most common variety, reduced absorption occurs when one or more passages connecting the ventricles become blocked. This prevents the movement of CSF to its drainage sites in the subarachnoid space just inside the skull. This type of hydrocephalus is called "noncommunicating." In a second type, a reduction in the absorption rate is caused by damage to the absorptive tissue. This variety is called "communicating hydrocephalus."

Both of these types lead to an elevation of the CSF pressure within the brain. This increased pressure pushes aside the soft tissues of the brain. This squeezes and distorts them. This process also results in damage to these tissues. In infants whose skull bones have not yet fused, the intracranial pressure is partly relieved by expansion of the skull, so that symptoms may not be as dramatic. Both types of elevated-pressure hydrocephalus may occur from infancy to adulthood.

A third type of hydrocephalus, called "normal pressure hydrocephalus," is marked by ventricle enlargement

KEY TERMS

Cerebral ventricles—Spaces in the brain that are located between portions of the brain and filled with cerebrospinal fluid.

Cerebrospinal fluid—Fluid that circulates throughout the cerebral ventricles and around the spinal cord within the spinal canal.

Choroid plexus—Specialized cells located in the ventricles of the brain that produce cerebrospinal fluid.

Fontanelle—One of several "soft spots" on the skull where the developing bones of the skull have yet to fuse.

Shunt—A small tube placed in a ventricle of the brain to direct cerebrospinal fluid away from the blockage into another part of the body.

Stenosis—The constricting or narrowing of an opening or passageway.

Subarachnoid space—The space between two membranes surrounding the brain, the arachnoid and pia mater.

without an apparent increase in CSF pressure. This type affects mainly the elderly.

Hydrocephalus has a variety of causes including:

- congenital brain defects
- hemorrhage, either into the ventricles or the subarachnoid space
- infection of the central nervous system (syphilis, herpes, meningitis, encephalitis, or mumps)
- tumor

Genetic profile

Hydrocephalus that is congenital (present at birth) is thought to be caused by a complex interaction of genetic and environmental factors. Aqueductal stenosis, an obstruction of the cerebral aqueduct, is the most frequent cause of congenital hydrocephalus. As of 2001, the genetic factors are not well understood. According to the British Association for Spina Bifida and Hydrocephalus, in very rare circumstances, hydrocephalus is due to hereditary factors, which might affect future generations.

Demographics

Hydrocephalus is believed to occur in approximately 1–2 of every 1,000 live births. The incidence of adult onset hydrocephalus is not known. There is no known way to prevent hydrocephalus.

Signs and symptoms

Signs and symptoms of elevated-pressure hydrocephalus include:

- headache
- nausea and vomiting, especially in the morning
- lethargy
- disturbances in walking (gait)
- double vision
- subtle difficulties in learning and memory
- delay in children achieving developmental milestones

Irritability is the most common sign of hydrocephalus in infants. If this is not treated, it may lead to lethargy. Bulging of the fontanelles, or the soft spots between the skull bones, may also be an early sign. When hydrocephalus occurs in infants, fusion of the skull bones is prevented. This leads to abnormal expansion of the skull.

Symptoms of normal pressure hydrocephalus include **dementia**, gait abnormalities, and incontinence (involuntary urination or bowel movements).

Diagnosis

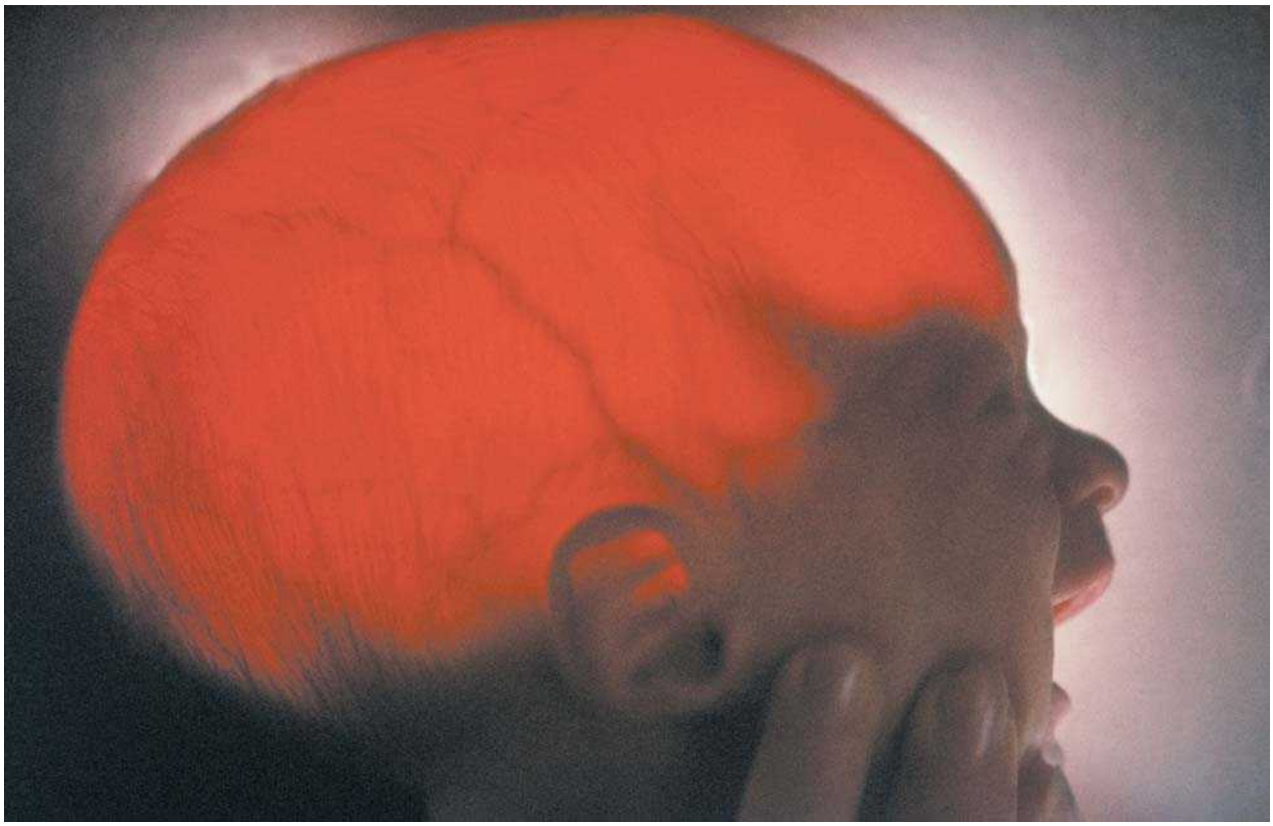
Imaging studies—x ray, computed tomography scan (CT scan), ultrasound, and especially magnetic resonance imaging (MRI)—are used to assess the presence and location of obstructions, as well as changes in brain tissue that have occurred as a result of the hydrocephalus. Lumbar puncture (spinal tap) may be performed to aid in determining the cause when infection is suspected.

Treatment and management

The primary method of treatment for both elevated and normal pressure hydrocephalus is surgical installation of a shunt. A shunt is a tube connecting the ventricles of the brain to an alternative drainage site, usually the abdominal cavity. A shunt contains a one-way valve to prevent reverse flow of fluid. In some cases of noncommunicating hydrocephalus, a direct connection can be made between one of the ventricles and the subarachnoid space, allowing drainage without a shunt.

Installation of a shunt requires lifelong monitoring by the recipient or family members for signs of recurring hydrocephalus due to obstruction or failure of the shunt. Other than monitoring, no other management activity is usually required.

Some drugs may postpone the need for surgery by inhibiting the production of CSF. These include acetazo-



Shining a bright light behind an infant with hydrocephalus, one can observe the excessive fluid accumulation in the skull. *(Corbis Corporation, Bellevue)*

lamide and furosemide. Other drugs that are used to delay surgery include glycerol, digoxin, and isosorbide.

Some cases of elevated pressure hydrocephalus may be avoided by preventing or treating the infectious diseases which precede them. Prenatal diagnosis of congenital brain malformation is often possible.

Prognosis

The prognosis for elevated-pressure hydrocephalus depends on a wide variety of factors, including the cause, age of onset, and the timing of surgery. Studies indicate that about half of all children who receive appropriate treatment and follow-up will develop IQs greater than 85. Those with hydrocephalus at birth do better than those with later onset due to meningitis. For individuals with normal pressure hydrocephalus, approximately half will benefit by the installation of a shunt.

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Association for Spina Bifida and Hydrocephalus. 42 Park Rd., Peterborough, PE1 2UQ UK. 0173 355 5988. Fax: 017 3355 5985. postmaster@asbah.org. <http://www.asbah.demon.co.uk>.

Columbia Presbyterian Medical Center. Dept. of Neurological Surgery, 710 West 168 St., New York, NY 10032. (212) 305-0378. Fax: (212) 305-3629. <http://cpmcnet.columbia.edu/dept/nsg/PNS/Hydrocephalus.html>.

Hydrocephalus Association. 870 Market St., Suite 705, San Francisco, CA 94102. (415) 732-7040 or (888) 598-3789. (415) 732-7044. hydroassoc@aol.com. <http://neurosurgery.mgh.harvard.edu/ha>.

Hydrocephalus Foundation, Inc. (HyFI), 910 Rear Broadway, Saugus, MA 01906. (781) 942-1161. HyFI1@netscape.net. <http://www.hydrocephalus.org>.

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L. Fleming Fallon, Jr., MD, DrPH

Hydrolethalus syndrome

Definition

Hydrolethalus syndrome is a rare disorder that results in severe birth defects and often, stillbirth.

Description

Hydrolethalus syndrome is a condition that causes improper fetal development. Multiple malformations along the body's midline, such as heart and brain defects, a cleft lip or palate, an abnormally shaped nose or jaw, and incomplete lung development result from this syndrome. The birth defects are typically extreme enough to cause stillbirth or death within a few days of birth. A less common name for hydrolethalus syndrome is Salonen-Herva-Norio syndrome, after the Finnish researchers who first described it in 1981.

Genetic profile

Hydrolethalus syndrome is passed on through an autosomal recessive pattern of **inheritance**. Autosomal means that the syndrome is not carried on a sex chromosome, while recessive means that both parents must carry the **gene mutation** in order for their child to have the disorder. Some cases of hydrolethalus syndrome have been observed in cases where the parents are related by blood (consanguineous). Parents with one child affected by hydrolethalus syndrome have a 25% chance that their next child will also be affected with the disease.

Each parent passes 23 **chromosomes**, or units of genetic information, to the infant. Structurally, each chromosome has a short segment or "arm," called the p arm, and a long arm, called the q arm, extending from a central region called the centromere. Along each arm the chromosome is further divided by numbering the bands down the arm according to their appearance under a microscope. Each band corresponds to specific genes. Based on studies of genetic material from affected and non-affected families, studies in 1999 assigned the gene location for hydrolethalus syndrome to 11q23-25, or somewhere between the 23rd and 25th band of the q arm of chromosome 11.

Demographics

The majority of cases of hydrolethalus syndrome have been reported in people of Finnish ancestry. In Finland the incidence of hydrolethalus syndrome is estimated at one in every 20,000. Less than twenty cases have been reported outside of Finland.

Hydrolethalus syndrome affects fetal development in the womb and is a syndrome of infants only, due to the extremely serious birth defects caused by the disorder. No cases of survival into childhood or adulthood have been reported. The syndrome appears to affect both males and females with equal probability.

Signs and symptoms

Prenatal symptoms include an excess of amniotic fluid in the womb (hydramnios). Babies with hydrolethalus syndrome are often delivered pre-term and may be stillborn.

After birth, the following conditions may be observed as a result of hydrolethalus syndrome:

- fluid in the skull and swelling leading to an abnormally large head (hydrocephalus)
- defects in the structure of the heart
- incomplete development of the lungs
- the presence of extra fingers and toes (polydactyly), especially an extra big toe or little finger
- **clubfoot**
- a cleft lip or palate
- a small lower jaw (micrognathia)
- abnormal eye and nose formation
- a keyhole-shaped defect at the back of the head
- abnormal genitalia

Diagnosis

Hydrolethalus syndrome can be diagnosed prenatally by ultrasound scanning in as early as the eleventh week of gestation. After birth, the presence of multiple malformations, especially the extreme swelling of the skull and other brain and spinal cord defects, can confirm the diagnosis. A family history and **genetic testing** may be useful in making the diagnosis certain.

KEY TERMS

Hydramnios—A condition in which there is too much amniotic fluid in the womb during pregnancy.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Micrognathy—Having a very small and receding jaw.

Polydactyly—The presence of extra fingers or toes.

Treatment and management

There is no treatment for hydrolethalus syndrome other than management of the specific medical conditions of the infant. **Genetic counseling** is particularly important in the prenatal treatment and management of hydrolethalus syndrome. This is because the severity of symptoms almost always causes death of the infant within a few days of birth, even if the fetus survives to full term.

Prognosis

The prognosis for infants with hydrolethalus syndrome is extremely poor. Most affected infants are stillborn or die within the first day of life. Only a handful of cases of survival past the neonatal period have been reported and the longest survival period was 44 days.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481 <http://www.rarediseases.org>.

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Paul A. Johnson

Hydrometrocolpos syndrome *see* **McKusick-Kaufman syndrome**

Hydrops fetalis

Definition

Refers to the abnormal accumulation of fluid in the skin, body cavities, umbilical cord, and placenta of an unborn baby. Hydrops fetalis (HF) can result from many different diseases and structural defects. HF is traditionally divided into two major categories: immune HF and nonimmune HF. Immune hydrops fetalis is caused by Rh incompatibility, and was the most common cause of HF until the advent of anti-Rh antibody treatment (RhoGAM®) during pregnancy. All other causes of HF are termed nonimmune HF. Nonimmune hydrops fetalis may be caused by chromosomal aberrations, other **genetic disorders**, infections, anemias, structural birth defects such as congenital heart disease, and many other conditions. Currently in the United States nonimmune HF consists of about 90% and immune HF consists of about 10% of cases.

Description

HF occurs when a baby has a condition or birth defect that causes accumulation of excess fluid, known as edema, in the skin and other body cavities. Immune HF occurs when a mother's blood group is Rh negative (this means that she does not have the Rh protein on the surface of her blood cells) and her baby's blood group is Rh positive (the baby has the Rh protein on its blood cells). During the pregnancy a small amount of the baby's blood crosses into the mother's circulatory system. When this happens, the mother's immune system recognizes the Rh protein on the baby's blood cells as foreign and makes antibodies to the Rh protein. The antibodies can then cross back over to the baby and attack its blood cells, destroying them and causing anemia. The anemia causes heart failure, subsequent edema, and, ultimately, HF. The mother's immune response becomes greater with each subsequent pregnancy in which the baby has Rh-positive blood and thus the HF becomes worse. Administration of anti-Rh antibodies during all of an Rh-negative mother's

KEY TERMS

Alpha-thalassemia—Autosomal recessive disorder where no functional hemoglobin is produced. Leads to severe untreatable anemia.

Arrhythmia—Abnormal heart rhythm, examples are a slow, fast, or irregular heart rate.

Congenital heart disease—Structural abnormality of the heart at birth. Examples include a ventricular septal defect and atrial septal defect.

Down syndrome—A genetic condition characterized by moderate to severe mental retardation, a characteristic facial appearance, and, in some individuals, abnormalities of some internal organs. Down syndrome is always caused by an extra copy of chromosome 21, or three rather than the normal two. For this reason, Down syndrome is also known as *trisomy 21*.

Gaucher disease—Autosomal recessive metabolic disorder caused by dysfunction of the lysosomal enzyme beta-glucosidase.

Lymphedema distichiasis—Autosomal dominant condition with abnormal or absent lymph vessels. Common signs include a double row of eyelashes (distichiasis) and edema of the limbs beginning around puberty.

Myotonic dystrophy—A form of muscular dystrophy, also known as Steinert's condition, characterized by delay in the ability to relax muscles after forceful contraction, wasting of muscles, as well as other abnormalities.

Pericardial cavity—Space occupied by the heart.

Pleural cavity—Area of the chest occupied by the lungs.

Sly disease—Autosomal recessive metabolic disorder caused by dysfunction of the lysosomal enzyme beta-glucuronidase.

Turner syndrome—Chromosome abnormality characterized by short stature and ovarian failure, caused by an absent X chromosome. Occurs only in females.

pregnancies will prevent her from ever developing an immune response to Rh-positive blood and thus will prevent HF.

The most common causes of nonimmune HF include heart disease (congenital malformations and arrhythmia), chromosome aberrations (**Turner syndrome** and **Down syndrome**), and anemia (alpha-thalassemia, fetomaternal transfusion, and twin-twin transfusion). Other causes include infections, metabolic disorders, and tumors. In all there are over 100 separate causes of nonimmune HF.

All disorders that cause HF do so by three common mechanisms that include heart failure, hypoproteinemia (low levels of protein in the blood stream), and vascular or lymphatic obstruction. Some disorders combine two or more of these mechanisms to cause HF. Most disorders cause some degree of heart failure. Anemia causes heart failure by increasing the work of the heart so much that it fails (this is termed high output heart failure). Isolated congenital heart disease or conditions that have congenital heart disease as a feature often will develop heart failure due to a poorly functioning heart (this is termed low output heart failure). Conditions that block the flow of blood or lymph can cause edema and HF. Examples include tumors and congenital malformations of the blood and lymphatic vessels. Conditions that lower that amount of protein in the blood can cause edema and HF by allowing fluid to easily leak out of the vessels and collect in the soft tissues and body cavities. Examples include metabolic conditions that damage the liver and prevent it from producing enough protein such as **Gaucher disease** and Sly disease.

Genetic profile

Many causes of hydrops fetalis do not have a genetic etiology. Because the recurrence risk can range from 0–100% depending on the underlying cause, an accurate diagnosis is important. Infectious causes are not genetic and should not recur in subsequent pregnancies. Other causes of HF have a specific genetic profile. Immune causes are due to a difference in the antigens on the mother and baby's blood cells. This can recur in subsequent pregnancies if anti-Rh antibodies are not given to the mother. Recurrence can either be 50% or 100% depending on the father's Rh-antigen status.

If hydrops fetalis is caused by a chromosome aberration, the risk of recurrence is about 1%, as most of these conditions occur sporadically and are not inherited. Malformations causing HF, such as congenital heart disease, are most commonly inherited as multifactorial traits. This type of **inheritance** pattern is caused by multiple genes and environmental factors working in combination. The recurrence risk for a multifactorial trait is about 3–5% with each subsequent pregnancy.

Higher risk for recurrence occurs when a single **gene** condition is the cause of HF. Autosomal recessive conditions such as alpha-thalassemia, Gaucher disease, and Sly disease have a recurrence risk of 25% with each subsequent pregnancy. The X-linked recessive disorder

G-6-P-deficiency has a recurrence risk of 50% with each additional male child and 0% for each additional female child.

Some dominant conditions can cause HF; these are often lethal and usually represent a new mutation in that child. In these cases the recurrence risk is about 1%. Other dominant conditions such as **myotonic dystrophy** and lymphedema distichiasis are variable and recurrence may be 50% with each child.

Demographics

The incidence of HF in the United States is 1 in 3,000 pregnancies in all populations. In developing countries where Rh antibodies are not used, the rate can be much higher, due to a higher rate of immune HF cases. In Southeast Asia the most common cause is alpha-thalassemia. Alpha-thalassemia is so common in Southeast Asia that it remains as the most common cause of HF in the world today.

Signs and symptoms

All babies with HF have edema of the skin, soft tissues, and placenta. Often the body cavities will show fluid collections including the abdominal cavity (ascites), pleural cavity, and pericardial cavity. The back of the neck is particularly prone to fluid collections and can sometimes contain so much fluid that it appears as a large cystic mass called a cystic hygroma. Internal organs such as the liver, spleen, and heart can become enlarged with accumulated fluid. All of these signs may be seen in the newborn or before birth using ultrasonography.

Other signs of hydrops fetalis are variable and often depend on the underlying cause. Common to most causes of HF are decreased movements during the pregnancy, respiratory distress from poor lung development due to compression of the lungs by accumulated fluid, and heart failure.

Diagnosis

HF is easily diagnosed at birth by the swollen appearance of an affected baby, but the diagnosis is often made during the pregnancy by ultrasonography. Determining the cause of the HF is more challenging, but necessary for possible treatment and recurrence risk assessment. Testing the mother for infections such as toxoplasmosis, rubella, cytomegalovirus (CMV), herpes, syphilis, and parvovirus B19 can rule out most infectious causes of HF. A high-resolution ultrasound will help determine if a baby has any major structural malformations or tumors that could cause HF. At the same time as the ultrasound a percutaneous umbilical artery blood sampling (PUBS) procedure can be done. This procedure consists of passing a needle through the mother's abdomen into the uterine cavity and then into the baby's umbilical cord to withdraw a small amount of blood. This blood is then used to test for Rh antibodies, anemia, chromosome aberrations, and other suspected conditions. These diagnostic steps will determine the cause for the HF in many cases, but sometimes the cause remains unknown.

Treatment and management

As discussed in the description section, immune HF is easily prevented by administration of anti-Rh antibodies to Rh negative pregnant women. Most nonimmune HF causes have no specific treatment other than early delivery and supportive care. HF caused by some types of anemia can be treated by a blood transfusion via a PUBS procedure. Fetal arrhythmia can often be treated by antiarrhythmia medications taken by the mother. Fetal operations are indicated for HF caused by sacrococcygeal teratomas (tumor seen in newborns) and some other structural malformations.

Prognosis

The prognosis is poor. A baby who is diagnosed by ultrasonography before birth has a less than 30% chance of survival. Babies who are born alive have a 50% chance of survival. The specific cause of HF influences the chances of survival with chromosome aberrations having a higher mortality rate and infectious etiologies having a lower mortality rate.

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Randall Stuart Colby, MD

Hyperactivity of childhood *see* **Attention deficit hyperactivity disorder (ADHD)**

Hyperglycinemia with ketoacidosis and lactic acidosis (propionic type) *see* **Propionic acidemia**

Hyperlipoproteinemia

Definition

Hyperlipoproteinemia refers to a group of acquired and inherited disorders whose common denominator is excessive levels of lipids (fats) in the blood, caused by a metabolic disorder. It is also referred to as hyperlipidemia. The condition is a major cause of coronary heart disease (CHD).

Description

The acquired form of hyperlipoproteinemia occurs as a condition secondary to another disease, such as **diabetes mellitus**, hypothyroidism, or nephrosis. The hereditary, or inherited, form of hyperlipoproteinemia is classified into five major types.

Lipids are an essential part of human metabolism and are a primary source of energy for the body. Lipids are produced by cells in the body and along with carbohydrates and proteins, are components of all life. But lipids are essentially oil-based and as such do not mix with a water-based liquid such as blood. Yet both must be carried through the body's circulatory system. So to get around this obstacle, lipids attach themselves to proteins. This combination of lipids and proteins is called lipoproteins, which are water-soluble particles that can be carried through the blood stream.

Some of the chemicals in the lipoproteins are fatty nutrients that are absorbed by the intestines for use in other parts of the body. Cholesterol is carried by lipoproteins through the blood stream to the liver and ultimately to the bowel for excretion. If the substances in the lipoproteins are not properly balanced, cholesterol will stay in the tissues instead of being excreted. It can also build up in blood vessels, eventually restricting and even blocking blood flow.

There are five different densities of lipoproteins, each containing triglycerides, cholesterol, phospholipids (lipids with phosphorus attached), and special proteins. The lipoproteins are high-density lipoproteins (HDL), low-density lipoproteins (LDL), intermediate-density lipoproteins, very low-density lipoproteins (VLDL), and chylomicrons. HDL is commonly called "good" cholesterol and LDL "bad" cholesterol. The two major lipoprotein groups are HDL and LDL.

HDL helps prevent fat buildup throughout the body by carrying cholesterol from the arteries to the liver, where it is disposed of. Abnormally low levels of HDL, fewer than 30 milligrams per deciliter (mg/dL) of blood, are associated with a greater risk for coronary heart disease and stroke. LDL carries most of the cholesterol in the body, so an excess of LDL, usually 160 mg/dL of blood, can clog the arteries with cholesterol buildup. This can lead to atherosclerosis, commonly referred to as hardening of the arteries, or acute myocardial infarction (heart attack).

The five types of inherited hyperlipoproteinemia are:

- Type I, characterized by high levels of chylomicrons and triglycerides and a deficiency of lipoprotein lipase, an enzyme that accelerates the breakdown of lipoproteins. Disease onset is usually in infancy.
- Type II, broken into two subtypes, type II-a and type II-b. Both subtypes display high levels of blood cholesterol. People with type II-b also have high levels of triglycerides in their blood. Disease onset is usually after age 20.
- Type III, also called broad beta disease, is characterized by high blood levels of cholesterol and triglycerides, and the presence of a lipoprotein called apolipoprotein E (apo E) genotype E2/E2. Disease onset is usually in adults.
- Type IV, characterized only by high triglyceride levels in the blood. Disease onset is usually during puberty or early adulthood.
- Type V, characterized by increased blood levels of chylomicrons and triglycerides and low levels of LDL and HDL. Disease onset is usually in children or adults.

Genetic profile

Type III hyperlipoproteinemia is an autosomal recessive disorder that affects males and females. Autosomal means that the **gene** does not reside on the sex chromosome. People with only one abnormal gene are carriers but since the gene is recessive, they do not have the disorder. Their children could be carriers of the disorder but not show symptoms of the disease. Both parents must have one of the abnormal genes for a child to have symptoms of type III hyperlipoproteinemia. When both parents have the abnormal gene, there is a 25% chance each child will inherit both abnormal genes and have the disease. There is a 50% chance each child will inherit one abnormal gene and become a carrier of the

disorder but not have the disease itself. There is a 25% chance each child will inherit neither abnormal gene and not have the disease nor be a carrier.

The other types of hyperlipoproteinemia are autosomal dominant. This means they occur when an abnormal gene from one parent is capable of causing the disease even though the matching gene from the other parent is normal. The abnormal gene dominates the outcome of the gene pair. This means that there is a 50% chance that each child of the couple will have the disease. Consequently, there is a 50% chance each child will not inherit the defective gene and will not have the disease.

Demographics

Hyperlipoproteinemia can affect people regardless of age, gender, race, or ethnicity. All adults, starting at age 20, should be tested for hyperlipoproteinemia at least once every five years, recommends the National Cholesterol Education Program (NCEP) of the National Institutes of Health (NIH). People considered at high risk for hyperlipoproteinemia should be tested more often and include those with a diet high in fat and cholesterol, have a family history of the disorder, use oral contraceptive or take estrogen, or who have diabetes mellitus, hypothyroidism, nephrosis, or **alcoholism**. Ethnic groups that have a higher risk of developing hyperlipoproteinemia include Latinos, Native Americans, African-Americans, and Pacific Islanders.

Signs and symptoms

It is very common for people with hyperlipoproteinemia to show no outward signs of the disorder. But there are several general signs that may indicate a person has the disorder, including obesity, yellowish skin, fatty yellow patches or nodules on the skin, especially the eyelids, neck, and back, inflamed tendons, an enlarged spleen, inflamed pancreas, nausea and vomiting, or abdominal pain. However, these are also symptoms of a variety of other conditions so for hyperlipoproteinemia to be diagnosed, blood tests are needed.

Diagnosis

Diagnosis involves a series of blood tests to measure lipid levels and determine the type of hyperlipoproteinemia. Blood tests, usually taken after a 12-hour fast, include measurement of total serum cholesterol, HDL, LDL, VLDL, triglycerides, and for the presence of apolipoprotein E. When hyperlipoproteinemia secondary to another disorder has been excluded and inherited hyperlipoproteinemia seems likely, first-degree relatives should be tested. These include parents, children, and siblings.

KEY TERMS

Atherosclerosis—Hardening of the arteries caused by cholesterol and fat deposits. Increases risk of heart disease, stroke, and other complications.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Chylomicrons—Microscopic lipid particles common in the blood during fat digestion and assimilation.

Diabetes mellitus—The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

Genetic—Referring to genes and characteristics inherited from parents.

Inflammation—Swelling and reddening of tissue; usually caused by immune system's response to the body's contact with an allergen.

Isotope—Any of two or more species of atoms of a chemical element with the same atomic number and nearly identical chemical behavior but with differing atomic mass and physical properties.

Nephrosis—A non-inflammatory disease of the kidneys.

Serum—The liquid part of blood, from which all the cells have been removed.

Treatment and management

Hyperlipoproteinemia treatment is usually based on a three-fold attack: diet, exercise, and lipid-lowering medications. People who are overweight should begin a program to slowly but consistently lose weight until they are at or near the recommended weight for their height and body frame. It is essential to eat a diet low in fat. Exercise also plays a vital role. A minimum of 20 minutes of aerobic exercise three times a week is beneficial and 30 minutes or more daily is ideal. The exercise can take the form of running, jogging, cycling, swimming, cardiovascular machines, or even walking briskly.

Eating healthy and exercising regularly, while extremely beneficial, are not always enough to bring lipid levels to the desired range. Prescription medications are often required. There is a wide range of medications

available to manage lipid levels. The most prescribed are HMG-CoA-reductase inhibitors, commonly called "statins," which hinder the body's production of cholesterol. Statins include cerivstatin (Baycol), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravacol), atorvastatin (Lipitor), and simvastatin (Zocor). Other first-line medications include bile acid sequestrants, cholestyramine (Questran), colesevelan (Welchol), and colestipol (Colestid). Also, probucol (Lorelco) is sometimes used.

The type of drug prescribed may vary, depending on the lipid test results and the type of hyperlipoproteinemia that is diagnosed. For example, people with type III of the disorder respond better when prescribed fibric acid derivatives such as gemfibrozil (Lopid), clofibrate (Atromid-S), and fenofibrate (Tricor) or nicotinic acid (niacin).

Other factors which have a negative effect on hyperlipoproteinemia include smoking, excessive alcohol consumption, and stress. It is also important to treat underlying conditions, such as diabetes, heart disease, pancreatitis (inflamed pancreas), and thyroid problems.

Prognosis

The prognosis is good for type I hyperlipoproteinemia with treatment. For type II, the prognosis is good for II-b and fair for II-a with early diagnosis and treatment. The prognosis for type III is good when the prescribed diet is strictly followed. The prognosis is uncertain for types IV and V, due to the risk of developing premature coronary artery disease in type IV and pancreatitis in type V.

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ORGANIZATIONS

Inherited High Cholesterol Foundation. University of Utah School of Medicine, 410 Chipeta Way, Room 167, Salt Lake City, UT 84104. (888) 244-2465.

National Cholesterol Education Program. National Heart, Lung and Blood Institute. PO Box 30105, Bethesda, MD 20824. (301) 592-8573. <http://www.nhlbi.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Ken R. Wells

Hypermobility syndrome *see* **Larsen syndrome**

Hypochondroplasia

Definition

Hypochondroplasia is an autosomal dominant mutation that results in short stature with disproportionately short arms and legs, but normal head size.

Description

Hypochondroplasia is a genetic form of short stature (dwarfism) due to a problem of bone growth and development. There are many causes for short stature including hormone imbalances, metabolic problems, and problems with bone growth. Hypochondroplasia is a common form of short stature and belongs to a class of dwarfism referred to as a chrondrodystrophy or skeletal **dysplasia**. All skeletal dysplasias are the result of a problem with bone formation or growth. There are over 100 different types of skeletal dysplasia.

Because the features of hypochondroplasia are so mild, the disorder may go undiagnosed. Although infants with hypochondroplasia may have low birth weight, hypochondroplasia is often not evident until between two and six years of age. In general, individuals with hypochondroplasia have disproportionate short stature with an average height of 51-57 in (130-145 cm). The degree of disproportion of the limbs to the body is variable.

Most individuals with hypochondroplasia have a normal IQ although some studies suggest that up to 10% of individuals with hypochondroplasia may have mild mental retardation or learning disabilities. This finding is controversial and more studies are currently underway to verify it. The motor development of infants with hypochondroplasia is normal. In rare cases, individuals with hypochondroplasia may experience neurologic problems due to spinal cord compression. The spinal

canal (which holds the spinal cord) can be smaller than normal in patients with hypochondroplasia.

Genetic profile

Hypochondroplasia is caused by a mutation, or change, in the fibroblast growth factor receptor 3 **gene** (FGFR3) located on the short arm of chromosome 4.

FGFR (fibroblast growth factor receptor) genes provide the instruction for the formation of a cell receptor. Every cell in the body has an outer layer called a cell membrane that serves as a filter. Substances are transported into and out of the cells by receptors located on the surface of the cell membrane. Every cell has hundreds of different types of receptors. The fibroblast growth factor receptors transport fibroblast growth factor into a cell. Fibroblast growth factors play a role in the normal growth and development of bones. When the receptors for fibroblast growth factor do not work properly, the cells do not receive enough fibroblast growth factor and the result is abnormal growth and development of bones.

Approximately 70% of hypochondroplasia is caused by mutations in the FGFR3 gene. The genes (or gene) responsible for the other 30% of cases are not known. The FGFR3 gene is comprised of 2,520 bases. In a normal (non-mutated) gene, base number 1620 codes for the amino acid asparagine. In most individuals with hypochondroplasia, a mutation changes the asparagine to the amino acid lysine. Two specific mutations account for approximately 70% of hypochondroplasia. These small substitutions change the amino acid that affects the protein structure. Both of these small substitutions cause a change in the fibroblast growth factor receptor (FGFR) that affects the function of this receptor.

The remaining 30% of patients diagnosed with hypochondroplasia do not show FGFR3 gene mutations. It has not yet been made clear if these patients have a different gene abnormality, an unrecognized FGFR3 **gene mutation**, or are normal variants. Another possibility is that these individuals actually have another disorder in which short stature results.

Mutations in the FGFR3 gene are inherited in an autosomal dominant manner. All people have two FGFR3 genes—one from their father and one from their mother. In an autosomal dominant disorder, only one gene has to have a mutation for a person to have the disorder. An individual with hypochondroplasia has a 50% chance of passing the changed (mutated) gene to his or her offspring. An individual can inherit a mutated gene from one parent or the mutation can occur for the first time in that person. Mutations that arise for the first time in affected individuals are called *de novo* mutations. The causes of mutations are not known.

KEY TERMS

Fibroblast growth factor receptor gene—A type of gene that codes for a cell membrane receptor involved in normal bone growth and development.

Rhizomelic—Disproportionate shortening of the upper part of a limb compared to the lower part of the limb.

Demographics

Because hypochondroplasia has such a wide range of variability, many people mildly affected with hypochondroplasia may never be diagnosed. Thus, the true incidence of hypochondroplasia is unknown. No studies have been done to determine the incidence of hypochondroplasia but it is assumed to be a relatively common disorder with an incidence equal to **achondroplasia**—one in 15,000 to one in 40,000.

Signs and symptoms

Individuals with hypochondroplasia have disproportionate short stature, limb abnormalities, and rhizomelic shortening of the limbs. Rhizomelic shortening of the limbs means that those segments of a limb closest to the body (the root of the limb) are more severely affected. In individuals with hypochondroplasia, the upper arms are shorter than the forearms and the upper leg (thigh) is shorter than the lower leg. In general, the upper limbs are more affected than the lower limbs in individuals with hypochondroplasia.

In addition to shortened limbs, individuals with hypochondroplasia have other characteristic limb differences such as a limited ability to rotate and extend their elbows. They can develop bowed legs, a finding that usually improves as they get older. Their hands and feet are short and broad, as are their fingers and toes. Their final adult height is usually 51-57 inches (130-145 cm). Their body habitus or shape is described as thick and stocky with a relatively long trunk. They may have lumbar lordosis (or curved back) giving them a swayed back appearance.

Diagnosis

The diagnosis of hypochondroplasia can be extremely difficult to make for a number of reasons. There is no one physical feature or x ray finding specific to hypochondroplasia and there is a great deal of overlap between individuals with hypochondroplasia and individ-

uals in the general population. Many of the physical findings of hypochondroplasia (short stature, bowed legs and a stocky build) are seen in individuals without hypochondroplasia. The same is true for the "typical" x ray findings. All of the possible x ray findings associated with hypochondroplasia can also be seen in unaffected individuals. There is no consensus on specific criteria necessary for diagnosis; however, it is usually made based on a combination of physical and x ray findings and is rarely made in infants.

DNA testing for hypochondroplasia is also complicated because testing will only detect 70% of the mutations that cause hypochondroplasia. DNA testing can be performed on blood samples from children or adults. If an individual is suspected of having hypochondroplasia and a mutation is detected, then the diagnosis is confirmed. If a mutation is not detected, then the diagnosis of hypochondroplasia has neither been confirmed nor ruled out. This individual could be one of the 30% of individuals with hypochondroplasia due to unknown mutations or he or she could have short stature due to another disorder.

Prenatal testing for hypochondroplasia can be performed using DNA technology. A sample of tissue from a fetus is obtained by either chorionic villus sampling (CVS) or by **amniocentesis**. Chorionic villus sampling is generally done between 10 and 12 weeks of pregnancy and amniocentesis is done between 16 and 18 weeks of pregnancy. Chorionic villus sampling involves removing a small amount of tissue from the developing placenta. The tissue in the placenta contains the same DNA as the fetus. Amniocentesis involves removing a small amount of fluid from around the fetus. This fluid contains some fetal skin cells. DNA can be isolated from these skin cells. The fetal DNA is then tested to determine if it contains either of the two mutations responsible for achondroplasia.

Prenatal DNA testing for hypochondroplasia is not routinely performed in low-risk pregnancies. This type of testing is generally limited to high-risk pregnancies, such as when one parent has hypochondroplasia. This testing can also only be performed if the mutation causing hypochondroplasia in the parent has been identified.

Treatment and management

There is no cure for hypochondroplasia. Because of the wide range of variability of this condition there is no consensus on the medical management of individuals with hypochondroplasia either. Individuals with more severe cases are the only individuals likely to need medical management. The recommendations for the medical management of individuals with achondroplasia have been outlined by the American Academy of Pediatrics' Committee on Genetics and should be used as a guide for the management of individuals with severe hypochondroplasia. The potential medical complications of hypochondroplasia range from mild to moderate. Early intervention may avert some of the long-term consequences of these complications.

As children with hypochondroplasia develop, certain conditions and behaviors should be monitored. Their height, weight, and head circumference should be measured regularly and plotted on growth curves developed for children with achondroplasia as a guide. Neurologic problems such as lethargy, abnormal reflexes, or loss of muscle control should be seen by a neurologist to make sure that they are not experiencing compression of their spinal cord. Compression of the spinal cord is rare in individuals with hypochondroplasia but can occur because of the abnormal size of their spinal canal.

Children with hypochondroplasia should also be monitored for sleep apnea. Sleep apnea occurs when an individual stops breathing during sleep. This can occur for several reasons including obstruction of the throat by the tonsils and adenoids, spinal cord compression, and obesity. Individuals with hypochondroplasia are more prone to sleep apnea due to the changes in their spinal canal and foramen magnum. Treatment for sleep apnea depends on the cause of the sleep apnea. Obstructive sleep apnea is treated by surgically removing the tonsils and adenoids. Weight management may also play a role in the treatment of sleep apnea.

The bowed legs of children with hypochondroplasia usually improve as they get older and rarely require surgical intervention. Children with hypochondroplasia can often have an increased risk for middle ear infections which can be treated with oral antibiotics and the surgical placement of ear tubes.

Children with visible physical differences can have difficulties in school and socially. Support groups such as Little People of America can be a source of guidance on how to deal with these issues. It is important that children with hypochondroplasia not be limited in activities that pose no danger.

Two treatments have been used to try to increase the final adult height of individuals with hypochondroplasia–limb-lengthening and growth hormone therapy. There are risks and benefits to both treatments and as of 2001, they are still considered experimental.

Limb-lengthening involves surgically attaching external rods to the long bones in the arms and legs. These rods run parallel to the bone on the outside of the body. Over a period of 18-24 months, the tension on these rods is increased which results in the lengthening of the underlying bone. This procedure is long, costly, and

has potential complications such as pain, infections, and nerve problems. Limb-lengthening can increase overall height by 12-14 in (30.5-35.6 cm). This is an elective surgery and individuals must decide for themselves if it would be of benefit to them. The optimal age to perform this surgery is not known.

Growth hormone therapy has been used to treat some children with hypochondroplasia. Originally there was doubt about the effectiveness of this treatment because children with hypochondroplasia are not growth hormone deficient. Studies have shown mixed results. Some children with hypochondroplasia show improvement in their growth rate and others do not. It is too early to say how effective this treatment is because the children involved in this study are still growing and have not reached their final adult height.

Prognosis

The prognosis for most people with hypochondroplasia is very good. In general, they have minimal medical problems, normal IQ, and most achieve success and have a long life regardless of their stature. The most serious medical barriers to an excellent prognosis are the neurologic complications that very rarely arise in hypochondroplasia, including mild mental retardation and spinal cord compression.

Successful social adaptation plays an important role in the ultimate success and happiness of an individual with hypochondroplasia. It is very important that the career and life choices of individuals with achondroplasia not be limited by preconceived ideas about their abilities.

Resources

ORGANIZATIONS

Human Growth Foundation. 997 Glen Cove Ave., Glen Head, NY 11545. (800) 451-6434. Fax: (516) 671-4055. <http://www. hgf1@hgfound.org>.

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408. (806) 737-8186 or (888) LPA-2001. lpadatabase@juno.com. <http://www.lpaonline.org>.

MAGIC Foundation for Children's Growth. 1327 N. Harlem Ave., Oak Park, IL 60302. (708) 383-0808 or (800) 362-4423. Fax: (708) 383-0899. mary@magicfoundation.org. <http://www.magicfoundation.org/ghd.html>.

WEBSITES

Human Growth Foundation. <http://www.hgfound.org/>.

Little People of America: An Organization for People of Short Stature. <http://www.lpaonline.org/lpa.html>.

MAGIC Foundation for Children's Growth. <http://www.magicfoundation.org>.

Kathleen Fergus, MS

Hypophosphatasia

Definition

Hypophosphatasia is an inherited bone disease whose clinical symptoms are highly variable, ranging from a profound lack of mineralization of bone with death occurring prior to delivery up to early loss of teeth in adulthood as the only sign. Still other affected individuals may have the characteristic biochemical abnormality but no outward clinical signs of the disorder. Hypophosphatasia is due to consistently low levels of an important enzyme in the body, alkaline phosphatase.

Description

The term hypophosphatasia was first coined in 1948 by a Canadian pediatrician, Dr. J.C. Rathbun. He used it to describe a male infant who developed and then died from severe rickets, weight loss, and seizures. Levels of the enzyme alkaline phosphatase were below normal in samples of blood and bone from this child.

Rickets is a condition resulting from a deficiency of vitamin D in children, causing inadequate strengthening of developing cartilage and newly formed bone. While this disorder shares many clinical characteristics with hypophosphatasia, the two conditions are separate and distinct. A major difference is that rickets are typically not lethal.

In 1953, the clinical features of hypophosphatasia were expanded to include not only abnormal mineralization of bone but also premature loss of the permanent teeth in adulthood. Since then, hypophosphatasia has been further divided into six different clinical forms. Each form is defined by the severity of the disease and the age at which symptoms first appear.

Alkaline phosphatase (ALP) is present in nearly all plants and animals. There are at least four different genes known to encode different forms of ALP in humans. Hypophosphatasia is due to a deficiency of the form of ALP that is particularly abundant in the liver, bones, and kidneys. This is often referred to as the tissue non-specific form of ALP, or TNSALP. This form of alkaline phosphatase is important in the mineralization, or hardening, of the bones of the skeleton as well as the teeth. Thus, abnormalities in either the production or function of this enzyme have a direct effect on the formation and strength of these parts of the body. In general, the more severe forms of hypophosphatasia are associated with lower serum TNSALP activity for that individual's age.

Genetic profile

The first report of siblings affected with hypophosphatasia was published in 1950, providing supportive evidence that it is an inherited abnormality as opposed to one that is acquired. This is an important distinction, particularly since rickets alone is often due to a lack of vitamin D in a person's diet. Good sources of vitamin D include fortified milk and sunlight. Rickets can therefore be an acquired medical problem.

Nearly all forms of hypophosphatasia are inherited as an autosomal recessive condition. In order to be affected, an individual must inherit two copies of a hypophosphatasia **gene**, or one copy from each carrier parent. Carriers have one normal gene and one hypophosphatasia gene and are typically asymptomatic. In some families, hypophosphatasia carriers have been found to have low to low-normal levels of TNSALP in their blood. As a general rule, however, it is difficult to detect carriers with biochemical tests due to the wide range of enzyme levels found among both carriers and non-carriers.

Two hypophosphatasia carriers face a risk of 25%, or a one in four chance, of both passing on the disease gene and having an affected child. On the other hand, there is a 75% chance that they will have an unaffected, normal child. These risks apply to each pregnancy.

In contrast, evidence suggests that some of the more mild adult forms of hypophosphatasia may be inherited as an autosomal dominant trait. In this mode of **inheritance**, a single copy of a hypophosphatasia gene can cause clinical abnormalities. An affected individual would consequently have a 50% risk of passing on the abnormal gene to each of his or her children.

The gene for TNSALP is located near the tip of the short arm of chromosome 1 at band 1p36.1-p34. Mutations in this gene are responsible for both the autosomal recessive and autosomal dominant forms of hypophosphatasia. Although it is not yet entirely clear how mutations in this gene cause impaired mineralization of bone, more recent work has shown that the type of mutation and its location within the gene each have an effect on the severity of disease. A wide range of mutations have been described to date. A common mutation for any form of hypophosphatasia has not yet been identified in most populations. Consequently, genetic analysis of TNSALP in most families requires extensive study of the entire gene.

Demographics

Hypophosphatasia has been described worldwide and is believed to occur in all races. The most severe form of the disease is estimated to occur in approximately one in every 100,000 liveborns. This corresponds to a carrier frequency of roughly one in every 200–300 individuals. The milder childhood and adult forms of hypophosphatasia are probably more common than the severe perinatal form.

Of note, hypophosphatasia is especially common among Mennonite families from Manitoba, Canada, where mating between blood relatives is not unusual. The frequency of severe disease in this population is approximately one in every 2,500 newborns with a corresponding carrier frequency of one in every 25. The number of mutations identified in this group is smaller than the general population.

Signs and symptoms

Each individual who has hypophosphatasia has clinical features derived from generalized impairment of skeletal mineralization. Six different clinical forms have been recognized. The prognosis associated with each form is dependent upon the severity of the disease and the age at which the condition is first recognized. Although affected individuals within a family tend to have similar abnormalities, it is possible to see clinical variability even between relatives.

Perinatal (lethal) hypophosphatasia

This is the most severe form of hypophosphatasia. Affected fetuses are often diagnosed during pregnancy with profound undermineralization of their bones. The limbs are typically shortened and abnormal. Bone fractures may be present. An excessive amount of amniotic fluid (polyhydramnios) during pregnancy is common. Many affected infants die prior to delivery, or are stillborn. Those who survive delivery are often irritable, have a high-pitched cry, and fail to gain weight. Respiratory failure is a common cause of death. This is usually due to deformities of the chest and associated underdevelopment of the lungs.

Infantile hypophosphatasia

Many infants with this form of the disease appear normal at birth and initially begin to develop normally. However, difficulties such as poor feeding and poor weight gain along with early clinical signs of rickets often begin before six months of age. Bony abnormalities of the chest as well as an increased susceptibility to fractures make affected infants more prone to developing pneumonia. Over 50% of affected children die during infancy, usually from severe respiratory failure. Those infants who do survive often suffer from episodes of recurrent vomiting and from abnormal kidney function due to excess loss of calcium from bone. Additionally,

they may develop a misshapen head due to early closure of specific bones of the skull. Spontaneous overall improvement in health has, however, also been reported.

Childhood hypophosphatasia

The most common clinical feature in this form of hypophosphatasia is loss of the primary (deciduous) teeth before the age of five. This premature loss is directly related to abnormal dental cementum. It is this structure that normally establishes the appropriate connection of the teeth to the jaw. In hypophosphatasia, it is frequently completely missing or present but either underdeveloped or abnormally developed.

Rickets is another feature commonly seen in this later onset form. Rickets frequently leads to delayed walking as a toddler, short stature, and a characteristic waddling gait. Other rachitic deformities may also be present such as bowed legs or enlargement of the wrists, knees, and ankles.

Adult hypophosphatasia

Most affected individuals are formally diagnosed in adulthood. However, a careful review of an individual's health often reveals a childhood history of rickets and early loss of the primary teeth. This is typically followed by relatively good health during adolescence and young adulthood.

Dental and skeletal abnormalities, however, gradually recur. The age at their onset as well as their severity varies between individuals. Early loss or even extraction of the permanent teeth is common. Other skeletal abnormalities, however, are of greater concern. Osteomalacia is a common complaint. Osteomalacia is the adult form of rickets. It is characterized by increasing softness of the bones. This, in turn, leads to increased flexibility and fragility and causes deformities. Clinically, osteomalacia is typified by chronic pain in the feet due to recurrent, poorly healing stress fractures. Affected adults may also experience discomfort in their thighs and hips from painful thin zones of decalcification (pseudofractures) in the bones of the thigh.

Odontohypophosphatasia

The only clinical abnormality associated with this form of hypophosphatasia is dental disease. It may occur in children or adults. Neither rickets nor osteomalacia has been found to occur.

Pseudo-, or false, hypophosphatasia

This is an especially rare clinical form documented in only a few infants. The physical features all resemble those seen in the infantile form of the disease. However, in contrast to all of the other forms of hypophosphatasia, the total alkaline phosphatase activity has been consistently normal or even increased in blood samples from the affected children. It is unclear what the exact biochemical or molecular abnormality is in these children.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Rachitic—Pertaining to, or affected by, rickets. Examples of rachitic deformities include curved long bones with prominent ends, a prominent middle chest wall, or bony nodules at the inner ends of the ribs.

Diagnosis

After birth, a diagnosis of hypophosphatasia is based on a combination of physical examination, x ray, and biochemical studies. X ray can be particularly helpful in differentiating between the more severe forms of hypophosphatasia (perinatal, infantile) and other inherited bone diseases. In the perinatal form, the skeleton generally appears completely undermineralized, occasionally absent. Bone fractures may be observed. The x-ray findings in the infantile form are similar to those seen in the perinatal form, but are usually much less severe.

Biochemical analysis may be performed on a routine blood sample. The serum may be used to determine the level of alkaline phosphatase activity. This usually represents TNSALP, and, in affected individuals, is generally low. However, it is important that the sample be obtained

and handled correctly in the laboratory so as not to interfere with the enzyme activity and raise the likelihood of an incorrect result. Also, the values from each individual should be interpreted carefully as variation normally occurs based on a person's sex and his or her age.

The genetic abnormality that causes hypophosphatasia leads to an inactive form of TNSALP in most cases. As a result, the chemicals on which the enzyme would normally act begin to accumulate, or increase, in the blood and urine. This accumulation is what hastens the defective calcification of bone. In theory, these substances could be measured to establish a diagnosis of hypophosphatasia. Although none have yet been proven to alone be reliable in all situations, a few appear more promising than others. These include pyridoxal-5-phosphate (PLP), phosphoethanolamine, or inorganic pyrophosphate. Abnormal (high) results lend further support to a diagnosis of hypophosphatasia when other clinical signs have also been recognized.

Prenatal diagnosis of hypophosphatasia has been successfully reported, although prior to the advent of molecular testing, it wasn't always completely reliable. Prenatal testing has been most widely used for the detection of the perinatal lethal form of hypophosphatasia. In some cases, the severe bone abnormalities of this type have been missed with a standard mid-pregnancy ultrasound but subsequently identified at an ultrasound performed much later. While this may be due, in part, to inexperience of the person performing the ultrasound, the highly variable clinical nature of hypophosphatasia is also to blame. A fetal x ray may be performed as a follow-up to any suspicious prenatal ultrasound evaluation.

Both chorionic villus sampling (CVS) and **amniocentesis** have been performed but have also on occasion been complicated by technical factors. For example, cultured cells from either a villus or amniotic fluid sample may be used to determine ALP activity. Because there are four forms of ALP in humans, the TNSALP form, which is abnormal in hypophosphatasia, may not be directly analyzed. An accurate interpretation of test results may therefore not be possible.

Direct analysis of the TNSALP gene thus holds the greatest promise for accurate prenatal diagnosis. Many different TNSALP mutations have been identified; many have been found in individual families only. It is also not unusual for two carrier parents to each have a different mutation. Direct analysis is therefore only currently possible for those families who have had at least one affected child and whose mutations have already been determined. Either CVS or amniocentesis may be used in these families for mutation studies. Rapid prenatal diagnosis of hypophosphatasia in the context of a negative family history is difficult.

Treatment and management

For those families in whom the underlying mutations are unknown, the most reliable method of prenatal diagnosis for perinatal lethal hypophosphatasia includes a combination of either CVS or amniocentesis for biochemical studies as well as serial ultrasound evaluations during pregnancy. If a diagnosis is made with certainty relatively early in pregnancy, the expectant parents should be offered the option of pregnancy termination.

As of 2001, there is no established, effective medical therapy for any form of hypophosphatasia. Care is mainly directed toward the prevention or correction of disease-related complications. Expert dental care is highly recommended for those individuals with dental abnormalities. Physical therapy and orthopedic management are important in the care and treatment of bone complications such as fractures. Young children with the infantile form should also be monitored carefully for increasing pressure within the head from early fusion of the bones of the skull. Traditional treatments for rickets or osteomalacia, such as vitamin D or other mineral supplements, should be avoided as these bone symptoms represent only one component of an inherited, rather than acquired, complex medical problem.

Prognosis

The prognosis associated with hypophosphatasia is directly related to the severity of the disease. In general, those individuals with the most severe skeletal abnormalities tend to do much worse than those with only mild clinical symptoms. Hence, infants who are diagnosed either during pregnancy or who have significant bone deformities at birth generally die within the first few days or weeks of life. These infants may also be stillborn. The prognosis associated with the infantile form of hypophosphatasia is variable: while over half of affected infants die during their first year due to serious breathing abnormalities, others spontaneously improve and may do well. Childhood disease is associated with skeletal deformities in some cases. Symptoms may improve, however, during adolescence only to occasionally reappear in adulthood. Finally, adult-onset hypophosphatasia is associated with ongoing, orthopedic problems once skeletal symptoms begin. Women, in particular, may notice increased bone loss and fractures after menopause.

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MAGIC Foundation for Children's Growth. 1327 N. Harlem Ave., Oak Park, IL 60302. (708) 383-0808 or (800) 362-4423. Fax: (708) 383-0899. mary@magicfoundation.org. <http://www.magicfoundation.org/ghd.html>.

National Institutes of Health, Osteoporosis and Related Bone Diseases. National Resource Center, 1232 22nd Street NW, Washington, DC 20037-1292. Fax: (202) 223-0344. <http://www.osteo.org/hypoph.html>.

WEBSITES

OMIM—Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov/omim>.

Terri A. Knutel, MS, CGC

Hypophosphatemia

Definition

Hypophosphatemia is a group of inherited disorders in which there is abnormally low levels of the substance phosphate in the blood, leading to softening of the bones. This condition can result in rickets, a childhood disease in which soft and weak bones can lead to the development of bone deformities. While there is no cure, treatment can prevent the bone changes and allow proper growth of bones.

Description

Bone is one of the strongest tissues of the human body. As the main component of the adult skeleton, it provides support for movement, protects the brain and organs of the chest from injury, and contains the bone marrow, where blood cells are formed. Bone is made up of several components, including a substance called hydroxyapatite. Hydroxyapatite is made of calcium and phosphate and is partially responsible for the strength of bone.

Because of the importance of hydroxyapatite, the strength of bone is dependent on the proper levels of calcium and phosphate within the body. A lack of calcium or phosphate in the diet or a failure in maintaining proper levels of calcium or phosphate in the blood can lead to abnormalities of bone growth. Another factor required for proper development of bone is vitamin D. Vitamin D is either obtained through foods in the diet, or is made by the body in response to sunlight exposure. Vitamin D is converted to another substance within the body called calcitriol. Calcitriol promotes bone development by helping to absorb calcium and phosphate from the diet and by preventing the loss of calcium and phosphate in the urine.

Hypophosphatemia is a group of inherited disorders in which there is abnormally low phosphate levels in the blood because large amounts of phosphate exit the body through the urine. In some forms of the disease there may also be problems in the conversion of vitamin D to calcitriol. Research suggests that inherited hypophosphatemia syndromes result from an abnormality in the way the kidney handles phosphate. Normally, the kidney prevents phosphate from leaving the body in the urine, but in hypophosphatemia, an abnormality in the way the kidney handles phosphate leads to large losses of phosphate in the urine. This results in abnormally low levels of phosphate in the blood, leading to poor hydroxyapatite formation and soft bones. Insufficient levels of phosphate for bone formation results in rickets, a childhood condition in which there is abnormal bone development, growth, and repair (when this occurs in adults, it is called osteomalacia). Inherited hypophosphatemia was first described by R. W. Winters in 1958 and has been referred to in the past as vitamin D-resistant rickets or familial hypophosphatemic rickets.

Genetic profile

Hypophosphatemia is a group of conditions that can be inherited or passed on in a family. The different types of hypophosphatemia have different causes, patterns of **inheritance**, and symptoms.

The most common and widely studied form of hypophosphatemia is hereditary hypophosphatemia type I, also known as X-linked hypophosphatemia (XLH). The abnormality in XLH is in a **gene** called PHEX. It is not known precisely how this gene affects phosphate handling by the kidney. Changes in other genes have been shown to cause hypophosphatemia, but the mechanism is similarly unclear. While most occurrences of hypophosphatemia are passed from parent to child, there are several examples of new genetic changes arising in a child with no relatives with hypophosphatemia.

There are different patterns of inheritance in different forms of hypophosphatemia, including autosomal dominant inheritance and X-linked dominant inheritance. In autosomal dominant inheritance, only one abnormal

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Calcitriol—A substance that assists in bone growth by helping to maintain calcium and phosphate levels in the blood. Vitamin D is converted into this substance by the body.

Calcium—One of the elements that make up the hydroxyapatite crystals found in bone.

Hydroxyapatite—A mineral that gives bone its rigid structure and strength. It is primarily composed of calcium and phosphate.

Hypophosphatemia—The state of having abnormally low levels of phosphate in the bloodstream.

Osteomalacia—The adult form of rickets, a lack of proper mineralization of bone.

Parathyroid glands—A pair of glands adjacent to the thyroid gland that primarily regulate blood calcium levels.

Phosphate—A substance composed of the elements phosphorus and oxygen that contributes to the hydroxyapatite crystals found in normal bones.

Rickets—A childhood disease caused by vitamin D deficiency, resulting in soft and malformed bones.

gene is needed to display the disease, and the chance of passing the gene to offspring is 50%.

X-linked dominant inheritance is similar to autosomal dominant inheritance in that only one abnormal gene is needed to display the disease. However, in X-linked dominant inheritance, the genetic abnormality is located on the X chromosome. Females have two X **chromosomes**, whereas males only have one X chromosome. Females have a 50% chance of passing the abnormal gene on to either a son or a daughter, as the mother always contributes one X chromosome to a child. On the other hand, males with the abnormal X chromosome will always pass the abnormal gene to a daughter (the father will contribute the abnormal X chromosome), but never to a son (the father will contribute a normal Y chromosome, and not the abnormal X chromosome)

Demographics

Hypophosphatemia has been estimated to be present in between one in 10,000 and one in 100,000 people, but one in 20,000 people is the most widely quoted figure. It is not known whether this disease is present equally among different geographical areas and ethnic groups. The first reports of the condition found hypophosphatemia in a Bedouin (nomadic Arab) tribe.

Signs and symptoms

Major symptoms of hypophosphatemia include poor growth, bone pain, abnormally bowed legs, weakness, tooth abscesses and sometimes listlessness and irritability in infants and young children. Although the disease affects all bones, the legs are more severely affected than the arms, ribs, or pelvis. The bowed legs are often noted by 12 months of age, and the altered growth increases in severity as the child grows older. Because of poor hydroxyapatite formation, people may experience fractures, and abnormal healing follows, further contributing to growth abnormalities. As a result of poor bone development and poor healing, people with hypophosphatemia often have short stature and may have a waddling walk. Other, less common manifestations of hypophosphatemia include high blood pressure and hearing loss or deafness.

While most symptoms are the same in the different types of hypophosphatemia, there may be small changes in the severity and age at which the person will experience the symptoms.

Diagnosis

If there is no family history of hypophosphatemia, diagnosis is usually guided by physical exam. Obvious bow leg deformities will lead to x rays of the legs and knees, which will show characteristic bone abnormalities. Other studies of bone strength using radioactive tracer materials can be used, or a bone biopsy (surgical excision of a small portion of bone for inspection with a microscope) can be performed to confirm that there is less hydroxyapatite than normal.

Laboratory tests aid in determining the cause of poor bone growth and rickets. In XLH, the serum phosphorus is low and the levels of serum calcium and calcitriol are low or sometimes normal. However, urine levels of phosphate are high, indicating that phosphate is being lost in the urine and that the kidney is not reabsorbing the phosphate properly. Another laboratory finding in XLH is the presence of increased alkaline phosphatase, a enzyme that breaks down bone. However, alkaline phosphatase is often elevated in growing children compared to normal adult values. Other forms of hypophosphatemia may have other variations in laboratory findings, including normal calcitriol levels or high levels of calcium in the urine and can be used to distinguish between the different types of hypophosphatemia.

Treatment and management

There is no cure, but medical and surgical treatment can greatly improve the outcome of people with hypophosphatemia. Goals of treatment include improvement in growth, reduction in severity of bone disease, bowed legs, and activity limitations, and minimizing the complications that may develop from the treatment itself.

Medical treatment is directed toward increasing the blood phosphate levels by using phosphate salts and calcitriol, both given by mouth. However, phosphate may have to be given five times a day because it is rapidly lost in the urine, and phosphate often causes diarrhea. Despite these drawbacks, the response to the medications is very good, and bowed legs may straighten over several years of growth. Scientific studies are also being performed to determine if growth hormone can help in achieving normal growth and height development.

Health care providers are able to monitor the person's ability to take the medication by checking the phosphate levels in the urine and the blood. It is recommended that these tests be performed in small children every three months to determine if they are receiving adequate amounts of phosphate. Later, the monitoring can be decreased to every four to six months. It is also recommended that childhood x rays of the knee be performed every one to two years to see whether medication changes are needed.

Some problems may result from the medications used to treat hypophosphatemia. High levels of calcium can build up in the bloodstream causing problems with the kidneys and the parathyroid (a gland in the neck). Because of these problems, routine calcium measurements and kidney ultrasound studies should be performed to determine if additional medications should be added or changes in medications should be made.

Treatment with medication is sometimes not enough to reverse the bone abnormalities. In cases such as these, surgery can be performed to reshape or even lengthen the bones.

Prognosis

With early diagnosis and treatment, the prognosis for people with hypophosphatemia is excellent. Adult heights of 170 cm may be achievable, compared to 130-165 cm without treatment. While some degree of abnormal bone growth may always be detectable, people with hypophosphatemia will generally live normal lifespans.

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Oren Traub, MD, PhD

Hypophosphatemic rickets *see* **Hypophosphatemia**

Hypospadias and epispadias

Definition

Hypospadias is a congenital defect, primarily of males, in which the urethra opens on the underside (ventrum) of the penis. The corresponding defect in females is an opening of the urethra into the vagina and is rare.

Epispadias (also called bladder exstrophy) is a congenital defect of males in which the urethra opens on the upper surface (dorsum) of the penis. The corresponding defect in females is a fissure in the upper wall of the urethra and is quite rare.

Description

In a male, the external opening of the urinary tract (external meatus) is normally located at the tip of the penis. In a female, it is normally located between the clitoris and the vagina.

In males with hypospadias, the urethra opens on the inferior surface or underside of the penis. In females with

KEY TERMS

Bladder—This is the organ that stores urine after it flows out of the kidneys and through the ureters.

Circumcision—The surgical removal of the foreskin of the penis.

Continence—Normal function of the urinary bladder and urethra, allowing fluid flow during urination and completely stopping flow at other times.

External meatus—The external opening through which urine and seminal fluid (in males only) leave the body.

Genital tract—The organs involved in reproduction. In a male, they include the penis, testicles, prostate and various tubular structures to transport seminal fluid and sperm. In a female, they include the clitoris, vagina, cervix, uterus, fallopian tubes and ovaries.

Urethra—The tubular portion of the urinary tract connecting the bladder and external meatus through which urine passes. In males, seminal fluid and sperm also pass through the urethra.

hypospadias, the urethra opens into the cavity of the vagina.

In males with epispadias, the urethra opens on the superior surface or upper side of the penis. In females with epispadias, there is a crack or fissure in the wall of the urethra and out of the body through an opening in the skin above the clitoris.

During the embryological development of males, a groove of tissue folds inward and then fuses to form a tube that becomes the urethra. Hypospadias occurs when the tube does not form or does not fuse completely. Epispadias is due to a defect in the tissue that folds inward to form the urethra.

During the development of a female, similar processes occur to form the urethra. The problem is usually insufficient length of the tube that becomes the urethra. As a result, the urethra opens in an abnormal location, resulting in a hypospadias. Occasionally, fissures form in the bladder. These may extend to the surface of the abdomen and fuse with the adjacent skin. This is most often identified as a defect in the bladder although it is technically an epispadias.

Hypospadias in males generally occur alone. Female hypospadias may be associated with abnormalities of the genital tract, since the urinary and genital tracts are formed in the same embryonic process.

Because it represents incomplete development of the penis, some experts think that insufficient male hormone may be responsible for hypospadias.

Genetic profile

Hypospadias and epispadias are congenital defects of the urinary tract. This means that they occur during intrauterine development. There is no genetic basis for the defects. Specific causes for hypospadias are not known. This means that blood relatives do not have increased chances of developing them.

Demographics

In males, the incidence of hypospadias is approximately one per 250 to 300 live births. Epispadias is much less common, having an incidence of about one per 100,000 live male births.

In females, hypospadias is much less common than in males. It appears about once in every 500,000 live female births. Epispadias is even rarer. Reliable estimates of the prevalence of epispadias in females are not available. Epispadias in females is often diagnosed and recorded as a bladder anomaly.

Signs and symptoms

Hypospadias is usually not associated with other defects of the penis or urethra. In males, it can occur at any site along the underside of the penis. In females, the urethra exits the body in an abnormal location. This is usually due to inadequate length of the urethra.

Epispadias is associated with bladder abnormalities. In females, the front wall of the bladder does not fuse or close. The bladder fissure may extend to the external abdominal wall. In such a rare case, the front of the pelvis is also widely separated. In males, the bladder fissure extends into the urethra and simply becomes an opening somewhere along the upper surface of the penis.

Hypospadias is associated with difficulty in assigning gender to babies. This occurs when gender is not obvious at birth because of deformities in the sex organs.

Diagnosis

Male external urinary tract defects are discovered at birth during the first detailed examination of the newborn. Female urethral defects may not be discovered for some time due to the difficulty in viewing the infant vagina.

Treatment and management

Surgery is the treatment of choice for both hypospadias and epispadias. All surgical repairs should be under-

taken early and completed without delay. This minimizes psychological trauma.

In males with hypospadias, one surgery is usually sufficient to repair the defect. With more complicated hypospadias (more than one abnormally situated urethral opening), multiple surgeries may be required. In females with hypospadias, surgical repair is technically more complicated but can usually be completed in a brief interval of time.

Repairing an epispadias is more difficult. In males, this may involve other structures in the penis. Males should not be circumcised since the foreskin is often needed for the repair. Unfortunately, choices may be required that affect the ability to inseminate a female partner. Reproduction requires that the urethral meatus be close to the tip of the penis. Cosmetic appearance and urinary continence are usually the primary goals. Surgery for these defects is successful 70 to 80% of the time. Modern treatment of complete male epispadias allows for an excellent genital appearance and achievement of urinary continence.

In females, repair of epispadias may require multiple surgical procedures. Urinary continence and cosmetic appearance are the usual primary considerations. Urinary continence is usually achieved although cosmetic appearance may be somewhat compromised. Fertility is not usually affected. Repair rates that are similar or better than those for males can usually be achieved for females.

Hypospadias in both males and females is more of a nuisance and hindrance to reproduction than a threat to health. If surgery is not an option, the condition may be allowed to persist. This usually leads to an increased risk of infections in the lower urinary tract.

Prognosis

With adequate surgical repair, most males with simple hypospadias can lead normal lives with a penis that appears and functions in a normal manner. This includes fathering children. Females with simple hypospadias also have normal lives, including conceiving and bearing children.

The prognosis for epispadias depends on the extent of the defect. Most males with relatively minor epispadias lead normal lives, including fathering children. As the extent of the defect increases, surgical reconstruction is generally acceptable. However, many of these men are unable to conceive children. Most epispadias in females can be surgically repaired. The chances of residual disfigurement increase as the extent of the epispadias increases. Fertility in females is not generally affected by epispadias.

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L. Fleming Fallon, Jr., MD, DrPH

I

Ichthyosis

Definition

Derived from the Greek word meaning fish disease, ichthyosis is a congenital (meaning present at birth) dermatological (skin) disease that is represented by thick, scaly skin.

Description

The ichthyoses are a group of genetic skin diseases caused by an abnormality in skin growth that results in drying and scaling. There are at least 20 types of ichthyosis. Ichthyosis can be more or less severe, sometimes accumulating thick scales and cracks that are painful and bleed. Ichthyosis is not contagious because it is inherited.

Genetic profile

Depending on the specific type of ichthyosis, the **inheritance** can be autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, or sporadic. Autosomal recessive means that the altered **gene** for the disease or trait is located on one of the first 22 pairs of **chromosomes**, which are also called "autosomes." Males and females are equally likely to have an autosomal recessive disease or trait. Recessive means that two copies of the altered gene are necessary to express the condition. Therefore, a child inherits one copy of the altered gene from each parent, who are called carriers (because they have only one copy of the altered gene). Since carriers do not express the altered gene, parents usually do not know they carry the altered gene that causes ichthyosis until they have an affected child. Carrier parents have a 1-in-4 chance (or 25%) with each pregnancy, to have a child with ichthyosis.

Autosomal dominant inheritance also means that both males and females are equally likely to have the disease but only one copy of the altered gene is necessary to have the condition. An individual with ichthyosis has a 50/50 chance to pass the condition to his or her child.

The last pair of human chromosomes, either two X (female) or one X and one Y (male) determines gender. X-linked means the altered gene causing the disease or trait is located on the X chromosome. Females have two X chromosomes while males have one X chromosome. The term "recessive" usually infers that two copies of a gene—one on each of the chromosome pair—are necessary to cause a disease or express a particular trait. X-linked recessive diseases are most often seen in males, however, because they have a single X chromosome, and no "back-up." So, if a male inherits a particular gene on the X, he expresses the altered gene, even though he has only a single copy of it. Females, on the other hand, have two X chromosomes, and therefore can carry a gene on one of their X chromosomes yet not express any symptoms. (Their second X, or "back-up," functions normally). Usually a mother carries the altered gene for X-linked recessive ichthyosis unknowingly, and has a 50/50 chance with each pregnancy to transmit the altered gene. If the child is a male, he will have ichthyosis, while if the child is a female, she will be a carrier for ichthyosis like her mother.

X-linked dominant inheritance means that only one gene from the X chromosome is necessary to produce the condition. Mothers with the altered gene are affected, and have a 50/50 chance to pass the condition to any child, who will also have ichthyosis. In somes cases, X-linked dominant inheritance is lethal in males, which means that male fetuses with X-linked dominant ichthyosis are miscarried. This is true for a rare disorder called Conradi-Hunerman, in which ichthyosis is just one feature.

New mutations—alterations in the **DNA** of a gene—can cause disease. In these cases, neither parent has the disease-causing mutation. This may occur because the mutation in the gene happened for the first time only in the egg or sperm for that particular pregnancy. New mutations are thought to happen by chance and are therefore referred to as "sporadic," meaning that they occur occasionally and are not predictable.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid which surrounds a developing baby during pregnancy.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Dermatologist—A physician that specializes in disorders of the skin.

Emollient—Petroleum or lanolin based skin lubricants.

Keratin—A tough, nonwater-soluble protein found in the nails, hair, and the outermost layer of skin. Human hair is made up largely of keratin.

Keratinocytes—Skin cells.

Keratolytic—An agent that dissolves or breaks down the outer layer of skin (keratins).

Retinoids—A derivative of synthetic vitamin A.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

X-linked dominant inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male or female, passed from an affected female who has the gene on one of her X chromosomes.

X-linked recessive inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male, passed from his mother who has the gene on one of her X chromosomes. She is referred to as an unaffected carrier.

Demographics

The most common form of ichthyosis is called ichthyosis vulgaris (*vulgar* is Latin for common), and occurs in approximately one person in every 250 and is inherited in an autosomal dominant manner. The most rare types of ichthyosis occur in fewer than one person in one million and are inherited in an autosomal recessive manner. Ichthyosis occurs regardless of the part of the world the child is from, or the ethnic background of the parents.

Signs and symptoms

The skin is made up of several layers, supported underneath by a layer of fat that is thicker or thinner depending on location. The lower layers contain blood vessels, the middle layers contain actively growing cells, and the upper layer consists of dead cells that serve as a barrier to the outside world. This barrier is nearly waterproof and highly resistant to infection. Scattered throughout the middle layers are hair follicles, oil and sweat glands, and nerve endings. The upper layer is constantly flaking off and being replaced from beneath by new tissue. In ichthyosis, the skin's natural shedding process is slowed or inhibited, and in some types, skin cells are produced too rapidly.

The abnormality in skin growth and hydration called ichthyosis may present with symptoms at birth or in early childhood. Ichthyosis can itch relentlessly, leading to such complications of scratching as lichen simplex (dermatitis characterized by raw patches of skin). Either the cracking or the scratching can introduce infection, bringing with it discomfort and complications.

Diagnosis

A dermatologist will often make the diagnosis of ichthyosis, based on a clinical exam. However, a skin biopsy, or DNA study (from a small blood sample) is necessary to confirm the diagnosis. Evaluation for associated problems is done by a complete physical medical examination.

For some types of ichythyosis, the abnormal gene has been identified and prenatal testing is available. At present this is true for the autosomal recessive congenital ichythoses, which includes: lamellar ichthyosis (LI), autosomal recessive lamellar ichthyosis (ARLI), congenital ichthyosiform erythroderm (CIE), and non-bullous congenital ichthyosiform erythroderma (NBCIE).

There are four different genes that have been located for the autosomal recessive congenital ichthyoses, however, testing is available for only one gene called transglutaminase-1 (TGM1) located on chromosome 14. Once a couple has had a child with ichthyosis, and they have had the genetic cause identified by DNA studies (performed from a small blood sample), prenatal testing for future pregnancies may be considered. (Note that prenatal testing may not be possible if both mutations cannot be identified.) Prenatal diagnosis is available via either

chorionic villus sampling (CVS) or **amniocentesis**. CVS is a biopsy of the placenta performed in the first trimester of pregnancy under ultrasound guidance. Ultrasound is the use of sound waves to visualize the developing fetus. The genetic makeup of the placenta is identical to the fetus and therefore the TGM1 gene can be studied from this tissue. There is approximately a 1 in 100 chance for miscarriage with CVS. Amniocentesis is a procedure done under ultrasound guidance in which a long thin needle is inserted through the mother's abdomen into the uterus, to withdraw a couple of tablespoons of amniotic fluid (fluid surrounding the developing baby) to study. The TGM1 gene can be studied using cells from the amniotic fluid. Other genetic tests, such as a chromosome analysis, may also be performed through either CVS or amniocentesis.

Treatment and management

Most treatments for ichthyosis are topical, which means they are applied directly to the skin, not taken internally. Some forms of ichthyosis requires two forms of treatment—a reduction in the amount of scale buildup and moisturizing of the underlying skin. Several agents are available for each purpose. Reduction in the amount of scale is achieved by keratolytics. Among this class of drugs are urea, lactic acid, and salicylic acid. Petrolatum, 60% propylene glycol, and glycerin are successful moisturizing agents, as are many commercially-available products. Increased humidity of the ambient air is also helpful in preventing skin dryness.

Because the skin acts as a barrier to the outside environment, medicines have a hard time penetrating, especially through the thick skin of the palms of the hands and the soles of the feet. This resistance is diminished greatly by maceration (softening the skin). Soaking hands in water macerates skin so that it looks like prune skin. Occlusion (covering) with rubber gloves or plastic wrap will also macerate skin. Applying medicines and then covering the skin with an occlusive dressing will facilitate entrance of the medicine and greatly magnify its effect.

Secondary treatments are necessary to control pruritus (itching) and infection. Commercial products containing camphor, menthol, eucalyptus oil, aloe, and similar substances are very effective as antipruritics. If the skin cracks deeply enough, a pathway for infection is created. Topical antibiotics like bacitracin are effective in prevention and in the early stages of these skin infections. Cleansing with hydrogen peroxide inhibits infection as well.

Finally, there are topical and internal derivatives of vitamin A called retinoids that improve skin growth and are used for severe cases of acne, ichthyosis, and other skin conditions.

Prognosis

This condition requires continuous care throughout a lifetime. Properly treated, in most cases it is a cosmetic problem. There are a small number of lethal forms, such as **harlequin fetus**.

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Foundation for Ichthyosis and Related Skin Types. 650 N. Cannon Ave., Suite 17, Landsdale, PA 19446. (215) 631-1411 or (800) 545-3286. Fax: (215) 631-1413. <http://www.scalyskin.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Catherine L. Tesla, MS, CGC

Ichthyosis bullosa of siemens *see* **Ichthyosis**

Ichthyosis congenita *see* **Ichthyosis**

Ichthyosis-spastic neurologic disorder-oligophrenia syndrome *see* **Sjögren Larsson syndrome**

Idiopathic basal ganglia calcification (IBGC) *see* **Fahr disease**

Incontinentia pigmenti

Definition

Incontinentia pigmenti (IP) is an X-linked dominant disorder affecting primarily the skin, hair, teeth and nails (all components of the epidermis). This disease may have been initially described by Garrod in 1906. It was completely characterized by Bloch and Sulzberger in 1928. For this reason, incontinentia pigmenti has also been referred to as Bloch-Sulzberger syndrome.

Description

Incontinentia pigmenti has been traditionally classified into two types: type I and type II. Much debate has occurred over whether or not type I, or sporadic, incontinentia pigmenti is actually the same disease as type II, or familial, male-lethal type, incontinentia pigmenti. The debate on this issue continues in the medical literature in early 2001. The growing consensus is that sporadic (type I) incontinentia pigmenti is not, in fact, the same disease as familial, male-lethal (type II) incontinentia pigmenti. Type II (familial, male-lethal) incontinentia pigmenti is considered to be the "classic" case of incontinentia pigmenti that matches the disease characterized by Bloch and Sulzberger in 1928.

Genetic profile

The locus of the **gene mutation** responsible for incontinentia pigmenti type II has been mapped to the long end of the X chromosome at gene location Xq28. The affected gene is known as the NEMO gene.

A chromosome is a long chain of deoxyribonucleic acid (**DNA**), a double-stranded molecule composed of individual units called nucleotides. The two strands that make up a single DNA molecule are held together by a matching (base pairing) of the nucleotides on one strand with the nucleotides on the other strand. Each set of a nucleotide on one strand paired with its nucleotide on the other strand is called a base pair.

A gene is a particular segment of a particular chromosome. Within the segment containing a particular gene there are two types of areas: introns and exons. Introns are sections of the particular chromosomal segment that do not actively participate in the functioning of the gene. Exons are those sections that do actively participate in gene function. A typical gene consists of several areas of exons divided by several areas of introns.

The NEMO gene was completely sequenced by the International Incontinentia Pigmenti Consortium in 2000. The NEMO gene consists of approximately 23,000 base pairs that compose 10 exons. The first exon of this gene, which is the exon that tells this gene to "turn on," has been found to have three variants; these are designated: 1a, 1b, and 1c.

The NEMO gene is known to partially overlap with the gene responsible for the production of glucose-6-phosphate dehydrogenase (G6PD). Mutations in the G6PD gene cause an under-production of red blood cells (anemia) that results in an insufficient amount of oxygen being delivered to the tissues and organs. Anemia resulting from mutations in the G6PD gene is observed with higher frequencies in Africans, Mediterraneans, and Asians.

The locus of the gene mutation responsible for type I incontinentia pigmenti has been mapped to band Xp11, on the short arm of the X chromosome. Individuals affected with this disorder show many of the signs of incontinentia pigmenti type II, but it is not an inherited condition. Type I incontinentia pigmenti is only exhibited as a sporadic and *de novo* trait. This means that when an affected individual has the symptoms of type I IP, that individual did not inherit this condition from his or her parents; rather the condition was caused by a mutation that occurred after conception.

Demographics

Incontinentia pigmenti is observed with higher frequencies in Africans, Mediterraneans, and Asians than in other portions of the population. This was originally thought to be due to the greater ability to observe the skin-related symptoms in these individuals. But, with the additional evidence that the NEMO gene and the G6PD gene overlap and that anemia resulting from mutations in the G6PD gene also disproportionately affects these populations, this anecdotal explanation has to be discarded.

More than 95% of all patients diagnosed with IP are female. The occurrence in males is probably due to a spontaneous (de novo) mutation in the NEMO gene that is not as severe as the typical mutation leading to IP or the misdiagnosis of type I IP. Approximately 70% of all IP affected individuals have been found to have the same

mutation in the NEMO gene. In these families, 100% lethality prior to birth is observed in males.

Signs and symptoms

Familial, male-lethal (type II) IP is characterized by progressive rashes of the skin. These have been classified into four stages: the red (erythematic) and blister-like (vesicular) stage; the wart-like (verrucous) stage; the darkened skin (hyperpigmented) stage; and the scarred (atrophic) stage.

The first, or erythematic vesicular, stage consists of patches of red skin containing blisters and/or boils. This condition usually appears in affected individuals at or near birth and is generally localized to the scalp, the arms, and the legs. This stage generally lasts from a few weeks to a few months and may recur within the first few months of life. It rarely recurs after the age of 6 months. This condition is often misdiagnosed as chicken pox, herpes, impetigo, or scabies. Each of these alternative diseases is potentially life-threatening in an infant, so most IP affected infants are treated for one of these diseases before the appropriate diagnosis of incontinentia pigmenti can be made.

The second, or verrucous, stage of IP is characterized by skin lesions that look like adolescent acne (pustules). Upon healing, these pustules generally leave darkened skin. This stage almost exclusively affects the arms and legs, but it may be observed elsewhere. The verrucous stage may occur at birth, which may indicate that the erythematic vesicular stage occurred prior to birth. But, more generally, the second stage of IP skin disorder is observed after the first stage has completed. The verrucous stage tends to persist for months. Rarely it may last for an entire year.

The third, or hyperpigmented, stage is characterized by "marbled skin," in which darkened areas of skin seem to make swirling patterns across the normal and less pigmented skin. This third stage generally occurs between six and 12 months of life. In 5-10% of affected individuals, this third stage is present at birth. These areas of hyperpigmentation tend to fade with age such that they are barely visible in adults affected with type II IP.

Areas of scarred skin caused by the first two stages characterize the fourth, or atrophic, stage. These scars are often noticeable before the third stage has begun to fade. Adolescents and adults affected with type II IP will generally have pale, hairless patches or streaks, most visibly on the scalp or calves, that are associated with this fourth stage. In many adults affected with IP, the skin abnormalities may have faded to such a significant degree that they are no longer noticeable to the casual observer. Many type II IP affected individuals have a loss or lack of hair on the crown of the head (alopecia). This is suspected to be caused by the underlying skin atrophies of IP.

More than 80% of individuals affected with type II IP have abnormalities of the teeth which include missing teeth, late eruption of both the baby teeth and the adult teeth, unusually pegged or cone-shaped teeth, and deficiencies in the enamel. A smaller percentage (approximately 40%) of affected individuals have irregular formations of the finger and toe nails including missing nails, thickened nails, and ridged or pitted nails. In a small number of cases, the skin lesions associated with the first two stages of skin abnormalities may be present

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

***de novo* mutation**—Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

Exon—The expressed portion of a gene. The exons of genes are those portions that actually chemically code for the protein or polypeptide that the gene is responsible for producing.

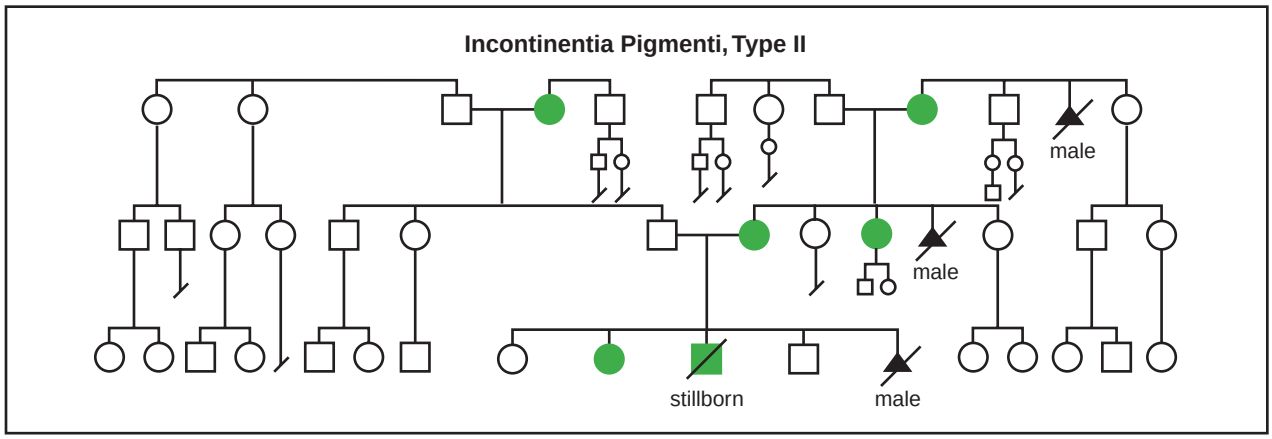
Hyperpigmentation—An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

Intron—That portion of the DNA sequence of a gene that is not directly involved in the formation of the chemical that the gene codes for.

Pustule—A pus-filled lesion of the skin that resembles the "pimples" of adolescent acne.

Type I incontinentia pigmenti—Sporadic IP. This disorder is caused by mutations in the gene at Xp11. These mutations are not inherited from the parents, they are *de novo* mutations. This type of IP probably represents a different disease than type II IP.

Type II incontinentia pigmenti—Familial, male-lethal type IP. This type of IP is the "classic" case of IP. It is caused by mutations in the NEMO gene located at Xq28. Inheritance is sex-linked recessive.



(Gale Group)

underneath a nail. In these cases, it is possible for this lesion to develop into a benign tumor that may cause abnormal bone development in the affected finger or toe.

Approximately 30% of all individuals affected with IP experience visual problems. Less than ten percent of type II IP affected individuals have vision problems related to an abnormal growth of blood vessels in the retina which may, if untreated, lead to a detachment of the retina possibly resulting in blindness. These symptoms generally are seen before the affected individual reaches the age of five. Other vision problems that have been observed in type II IP affected individuals include crossed eyes or "wall eyes" resulting from an improper alignment of the eyes (strabismus); partial or complete opaqueness in one or both lens (cataract); and, occasionally abnormally small eyes (microphthalmia). Because of these vision problems, some individuals affected with IP are blind at birth or will go blind if corrective treatment is not sought.

The incidence of breast development anomalies in type II IP affected girls is quite common. It is estimated to be more than ten times that of the general population. These anomalies range from the presence of an extra nipple to the complete absence of breasts.

Approximately 25% of all IP affected individuals have disorders of the central nervous system. These include mental retardation, slow motor development, **epilepsy**, an abnormally small brain (microcephaly) and increased muscle tone in both legs (spastic diplegia) or in all four limbs (spastic tetraplegia) similar to that seen in the classic case of **cerebral palsy**.

Diagnosis

The genetic mutation responsible for type I incontinentia pigmenti has been fully mapped and sequenced; therefore, it is possible to perform a genetic test for the existence of this disease. However, most cases are still diagnosed on a clinical basis.

Clinical diagnosis of type I IP is based primarily on the skin abnormalities seen at birth. These skin problems may still be misdiagnosed as chicken pox or herpes. This misdiagnosis is easily corrected when the affected individual begins to develop the later stages of the skin anomalies. All suspected male infants should have a chromosome test performed to confirm diagnosis.

In older patients with scarred skin, a skin biopsy that shows "loose" melanin (the pigment that produces color in the skin) confirms a diagnosis of IP.

When the skin appears normal, a diagnosis of IP is indicated when an individual shows one or more of the physical symptoms characteristic of IP: teeth abnormalities, missing patches of hair (alopecia), and/or overgrowth and scarring of the retinal blood vessels; and, that individual is female, has two or more IP affected daughters, is the daughter or sister of an affected woman, or has experienced the miscarriage of two or more male fetuses.

The presence of seizures within the first weeks of life indicate central nervous system involvement in the IP affected individual and indicate an extremely high likelihood of subsequent developmental delay.

Treatment and management

Usually no treatment for the skin conditions associated with IP is necessary other than the control of secondary infection that may occur.

In a female newborn where IP is suspected, an eye exam to look for retinal abnormalities, or any of the other possible eye disorders associated with IP, should be conducted within the first few days after birth. Older affected

individuals should have regular eye exams to ensure that retinal abnormalities do not develop. Laser treatments and freezing treatments (cryopexie) are often required to prevent retinal detachment.

Dental treatment is often necessary to repair damaged enamel or for cosmetic reasons in the cases of missing teeth or abnormally shaped teeth.

In cases where there is involvement of the central nervous system, the necessary treatments are on a symptomatic basis. These may include early and continuing intervention programs for developmental delays, anticonvulsants to control seizures, muscle relaxants to control spasticity, and/or surgery to release the permanent muscle, tendon, and ligament tightening (contracture) at the joints that is characteristic of longer term spasticity.

Prognosis

Incontinentia pigmenti is generally fatal in males prior to birth. Females, and the few surviving males, who are affected with IP can expect a normal lifespan if treatment is undertaken to repair or manage any of the associated symptoms.

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National Incontinentia Pigmenti Foundation. 30 East 72nd St., New York, NY 10021. (212) 452-1231. Fax: (212) 452-1406. <http://imgen.bcm.tmc.edu/NIPF>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paul A. Johnson

Infantile autism *see* **Autism**

Infantile refsum disease

Definition

Infantile refsum disease (IRD) is an inherited disorder characterized by the reduction or absence of cellular peroxisomes and by the accumulation of various unmetabolized substances in the blood and bodily tissues. The disorder arises in infancy and results in visual and hearing impairments, decreased muscle tone, poor growth, mental retardation, decreased coordination, liver damage, and abnormal development of facial structures. There is no cure for the disorder, and treatment is limited to the relief of symptoms.

Description

Living bodies are built up of millions of individual cells specifically adapted to carry out particular functions. Within cells are even smaller structures, called organelles, which perform different jobs and enable the cell to serve its ultimate purpose. One type of organelle is the peroxisome, whose function is to break down waste materials or to process materials that, if allowed to accumulate, would prove toxic to the cells.

Peroxisomes break down various materials through the use of enzymes (proteins that assist in biochemical reactions), and 80 different peroxisomal enzymes have been identified. These enzymes are made by the cell and transported into the peroxisome by a complex process, requiring at least 15 other proteins. In some cases, an absence or deficiency of these proteins results in a failure to transport enzymes into peroxisomes, leaving the cell unable to metabolize various substances. These substances build up in the blood stream and deposit in various tissues, causing damage.

Infantile refsum disease (IRD) results from an abnormality in the transport of enzymes into the peroxisome, manifesting as absent or reduced functioning peroxisomes. As a consequence of peroxisome deficiency, various substances accumulate in the bloodstream, including phytanic acid, pipecolic acid, hydroxycholestanoic acids, glyoxylate, and substances called very-long-chain fatty acids (VLCFA). Mutations in at least two different genes that encode proteins that participate in the transport of enzymes to the peroxisome have been identified in IRD.

IRD is thought to be the mildest form of leukodystrophy, a group of **genetic disorders** including **Zellweger syndrome** and neonatal **adrenoleukodystrophy**, that damage the fatty sheaths surrounding nerves. In the past, IRD was thought to be a variant of adult **refsum disease** (also called classical refsum disease) because

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Cerebellar ataxia—Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Mutation—A change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease.

Organelle—Small, sub-cellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

Peripheral neuropathy—Any disease of the nerves outside of the spinal cord, usually resulting in weakness and/or numbness.

Peroxisome—A cellular organelle containing different enzymes responsible for the breakdown of waste or other products.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

both disorders demonstrate high levels of phytanic acid due to a peroxisomal abnormality. However, later studies demonstrated that the peroxisomal abnormality in IRD is global, affecting many different enzymes, as opposed to the abnormality in adult refsum disease, where only one specific peroxisomal enzyme is abnormal. Indeed, people with IRD show the accumulation of many substances in their bloodstream in addition to phytanic acid and experience different and more severe symptoms than those experienced by people with adult refsum disease. Currently, the two diseases are regarded as separate and distinct entities with different genetic, biochemical, and clinical profiles.

Genetic profile

IRD is a genetic condition and is inherited or passed on in a family. The genetic abnormality for the disorder is inherited as an autosomal recessive trait, meaning that two mutant genes are needed to display the disease. A person who carries one mutant **gene** does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to their children. A child must inherit the same abnormal gene from each parent to display the disease.

IRD is caused by an abnormality in proteins that assist in the transport of enzymes into the peroxisome. Mutations in the genes for at least two different peroxisomal transport proteins have been identified. The first gene is designated PEX1 (mapped to human chromosome 7, locus 7q21-q22) and encodes for a protein called peroxisome biogenesis factor-1. The second gene is designated PEX2 (mapped to human chromosome 8, locus 8q21.1) and encodes for a protein called peroxisomal membrane protein-3.

Demographics

The combined incidence of all leukodystrophy disorders is estimated to be between 1 in 25,000 and 1 in 50,000. It is unclear whether these disorders are distributed equally among different geographical areas and ethnic groups. Because of some overlap with other leukodystrophy disorders, the incidence and prevalence of IRD in the general population is not clear.

Signs and symptoms

Symptoms associated with IRD arise at birth or very early infancy and affect many different organ systems and tissues, resulting in severe disease. Babies with IRD show decreased muscle tone and a failure to grow at appropriate rates. Characteristic facial features are often present, including prominent forehead and folds at the inner aspect of the eye, flat face and bridge of the nose, and low-set ears. While affected children are able to walk, the gait may be irregular due to abnormalities in muscle coordination.

High levels of unmetabolized substances can deposit in the fatty sheaths surrounding nerves, causing damage and resulting in peripheral neuropathy. Peripheral neuropathy is the term for dysfunction of the nerves outside of the spinal cord, causing loss of sensation, muscle weakness, pain, and loss of reflexes. Nerves leading to the ears can be affected, resulting in hearing loss or deafness. IRD also results in cerebellar ataxia, an abnormality in a specific part of the brain (the cerebellum), resulting in loss of coordination and unsteadiness. In contrast to adult refsum disease, people with IRD have extensive impairments in cognitive function resulting in severe mental retardation.

IRD often affects the eyes, causing **retinitis pigmentosa**, a degeneration of the retina resulting in poor nighttime vision, followed by loss of peripheral vision and eventually loss of central vision late in the course of the disease. Nystagmus (uncontrollable movements of the eye) may also be present due to related nervous system damage. Other manifestations of IRD include enlargement of the liver, poor digestion, and abnormally low blood cholesterol. Early osteoporosis (decalcifications of the bone) may also develop, leading to bone fractures or compression of the spinal bones.

Diagnosis

IRD is diagnosed though a combination of consistent medical history, physical exam findings, and laboratory and **genetic testing**. Typically, parents bring newborns to their physicians because of the signs of low muscle tone. Other times, the characteristic facial abnormalities or a failure to grow at appropriate rates is noted. These findings raise suspicion for a genetic syndrome or metabolic disorder, and further tests are conducted.

Laboratory tests reveal several abnormalities. Blood samples from patients with IRD show accumulation of various substances including phytanic acid, pipecolic acid, hydroxycholestanoic acids, glyoxylate, and VLCFA. Other measurements demonstrate low levels of plasmalogen, a substance normally produced by action of the peroxisomal enzymes. Immunoblot tests that measure levels of specific proteins will show deficiencies in many peroxisomal enzymes. Additional studies will reveal abnormal electrical responses from the retina and various nerve groups.

Finally, genetic testing can be preformed. When a diagnosis of IRD is made in a child, genetic testing of the PEX1 and PEX2 genes can be offered to determine if a specific gene change can be identified. If a specific change is identified, carrier testing can be offered to relatives. In families where the parents have been identified to be carriers of the abnormal gene, diagnosis of IRD before birth is possible. Prenatal diagnosis is performed on cells obtained by **amniocentesis** (withdrawal of the fluid surrounding a fetus in the womb using a needle) at about 16-18 weeks of pregnancy or by chorionic villus sampling (CVS) where cells are obtained from the chorionic villi (a part of the placenta) at 10-12 weeks of pregnancy.

Treatment and management

There is no cure or standard course of treatment for IRD. Currently, treatment of patients has generally involved only supportive care and symptomatic therapy. Several studies suggest that a diet that is free of phytanic acid can limit symptoms of IRD, but this is not nearly effective as in adult refsum disease. A useful adjunct to dietary treatment is plasmapheresis. Plasmapheresis is a procedure by which determined amounts of plasma (the fluid component of blood that contains the unmetabolized substances) is removed from the blood and replaced with fluids or plasma that are free of accumulated substances. While treatment strategies may mitigate some of the symptoms experienced by the patient with IRD, they do not slow the progression of the disorder.

Experimental studies are underway to investigate whether several different agents can be of additional use. Patients with IRD have reduced levels of docosahexaenoic acid and arachidonic acid that can be corrected with the administration of oral supplements. There are some reports of improvement in symptoms with these therapies, and trials to formally investigate these claims are now in progress. Other scientific laboratories are investigating the usefulness of agents that stabilize peroxisomes in the treatment of IRD, but the experiments are still in their early stages.

Patients with IRD should be seen regularly by a multidisciplinary team of health care providers, including a pediatrician, neurologist, ophthalmologist, cardiologist, medical geneticist specializing in metabolic disease, nutritionist, and physical/occupational therapist. **Genetic counseling** can help people with IRD, those who are carriers of the abnormal gene, or those who have a relative with the disorder, learn more about the disease, **inheritance**, testing, and options available to them so they can make informed decisions appropriate to their families.

Prognosis

For patients with IRD, some success has been achieved with multidisciplinary early intervention, including physical and occupational therapy, hearing aids, alternative communication, nutrition, and support for the parents. Although most patients continue to function in the profoundly or severely retarded range, some make significant gains in self-help skills, and a small percentage may reach stable condition in their teens. Despite these few successes, the prognosis for individuals with IRD is poor; death generally occurs in the second decade of life.

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ORGANIZATIONS

Infantile Refsum disease support and information. 6004 NE 108th Avenue, Vancouver, WA, 98662. (360) 891-5878. <http://home.pacifier.com/~mstephe/>.

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Infantile Refsum's Disease Webring. <http://www.angelfire.com/nc/homefireplace/IRDring.html>.

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Oren Traub, MD, PhD

Inheritance

Definition

Inheritance refers to the transmission of genetic information across generations. There are two types of inheritance patterns in humans: Mendelian nuclear inheritance and non-Mendelian mitochondrial inheritance. The 23 pairs of human **chromosomes** located in the nucleus of the cells make up the human nuclear genome. This genome contains an estimated 30 to 40 thousand genes that we inherit in combination from our parents. These genes are called Mendelian-inherited nuclear genes, after Gregor Mendel, the Austrian monk who first established the laws of inheritance in the late 1800s. There is also **DNA**, called mitochondrial DNA, or the mitochondrial human genome, in the cytoplasm that we inherit almost exclusively from our mothers. These mitochondrial genes are called non-Mendelian-inherited mitochondrial genes.

Mendelian inheritance

Mendelian type inheritance is the more familiar form of genetic inheritance. During reproduction, genetic material is passed from the mother and the father to the offspring. These genes are inherited according to the laws of segregation established by Gregor Mendel, and are called Mendelian-inherited nuclear genes.

A chromosomally normal human carries 23 pairs of chromosomes in the nucleus of each cell: 22 pairs of autosomes and one pair of sex chromosomes. An individual inherits one of each paired chromosome from each parent. Each of these chromosomes is made up of thousands of genes. Genes are the chemical sequences which together control all characteristics and functions of the body. A particular characteristic controlled by a single **gene** is called a trait.

Almost all genes are located on each of the two copies of the paired chromosomes. The two copies of these genes, taken together, are called an allele. If the two copies of this gene are identical to each other, this person is said to have a homozygous allele for that gene. If the two copies of this gene are not the same, this person is said to have a heterozygous allele for that gene.

The only genes that are not located on two copies of paired chromosomes occur when there is not a matching pair of chromosomes, such as those genes on the single X chromosome in an XY male. When only one chromosome carries a gene, this gene is called a hemizygous allele. A hemizygous allele is made up of only the one copy that is present.

There are three modes of Mendelian inheritance: dominant, semi-dominant, and recessive. Additionally, a trait may be sex-linked, or non-sex-linked (autosomal). A sex-linked trait is conferred from parents to their child on the X or Y chromosome. An autosomal trait is transmitted from parents to their child on one of the other 22 pairs of chromosomes (the autosomes).

Recent advances in molecular genetics have tended to blur the line between dominant and semi-dominant inheritance. It is now believed that semi-dominant inheritance is almost always observed in traits once felt to be strictly dominant traits. These research findings are in direct opposition to current clinical practice. Genetic counselors and other health care professionals prefer not to confuse their patients by referring to semi-dominant inheritance of a particular trait. Therefore, in a research setting, one is unlikely to discuss true dominance of a trait, while in a clinical setting, one is unlikely to encounter the usage of semi-dominance.

Autosomal Mendelian inheritance

AUTOSOMAL DOMINANT In autosomal dominant inheritance, only one copy of the gene that causes a specific trait must be present in order for the person to display (express) the trait. The gene is said to dominate the expression of the trait because its effects outweigh that of

the corresponding gene on the other half of the chromosome pair. Thus, in the case of a genetic mutation, one parent may pass the mutation to his or her offspring. Homozygous and heterozygous individuals will be affected equally by the mutation and both will express identical forms of the trait. The second copy of the mutated gene in the homozygous individual does not affect them more severely than the single copy of the mutated gene affects the heterozygous individual.

By definition, parents who pass on an autosomal dominant mutation to their offspring express the characteristics of that mutation. These parents are not called carriers because they are already fully affected with the trait. In the case of one heterozygous affected parent, the probability that a child will inherit this trait is 50%. In the case of two heterozygous affected parents, the probability that a child will inherit this trait is 75%. In the case of one homozygous affected parent, regardless of whether or not the other parent is affected, the probability that a child will inherit this trait is 100%.

AUTOSOMAL SEMI-DOMINANT If a particular trait is an autosomal semi-dominant trait, homozygous and heterozygous individuals will both experience characteristics of the trait. The gene for this trait still dominates the expression of the trait, but the effect of the corresponding gene on the other chromosome is noticeable. In diseases caused by a genetic mutation, the homozygous individual will experience more severe characteristics of that disease than the heterozygous individual because of the extra copy of the mutated gene that the homozygous individual possesses. Heterozygous individuals are carriers of the trait. Because these heterozygous individuals will exhibit some symptoms of the trait, they are also called symptomatic carriers.

In the case of one carrier parent and one non-carrier parent, the probability that a child of these parents will be a carrier of the trait is 50%, but their child cannot be homozygous for the trait. In the case of a homozygous affected parent and a non-carrier parent, the probability of a child being homozygous for the trait is also zero. The probability that this child will be a carrier of the trait is, however, 100%. In the case of two carrier parents, the probability that a child will be homozygous for the trait is 25%. The probability that this child will be a symptomatic carrier is 50%. In the case of one carrier parent and one affected parent, the probability that a child will be affected is 50%. The probability that this child will be a symptomatic carrier is also 50%. In the case of two affected parents, the probability that a child will be affected is 100%.

AUTOSOMAL RECESSIVE If a particular trait is an autosomal recessive trait, two copies of the mutated gene that causes this trait must be present in order for the person to possess the trait. The effect of the recessive gene is less than that of the corresponding gene on the other half of the chromosome pair. Therefore, only homozygous individuals will be affected with the trait. Heterozygous individuals will not exhibit characteristics of the trait. These heterozygous individuals are called carriers because they carry the trait and can pass it on to their children. Because these heterozygous individuals do not show characteristics of the trait that they carry, they are also called asymptomatic carriers.

A child cannot exhibit the symptoms of a recessive trait unless her or his parents are either both carriers of the trait or one is a carrier of the trait and the other is affected with the trait. In the case of one carrier parent and one non-carrier parent, the probability of a child being affected with the trait is zero. However, the probability that a child of these parents will be a carrier of the trait is 50%. In the case of an affected parent and a non-carrier parent, the probability of a child being affected with the trait is also zero. The probability that this child will be a carrier of the trait is, however, 100%. In the case of two carrier parents, the probability that a child will be affected with the trait is 25%. The probability that this child will be an asymptomatic carrier is 50%. In the case of one carrier parent and one affected parent, the probability that a child will be affected is 50%. The probability that this child will be an asymptomatic carrier is also 50%. In the case of two affected parents, the probability that a child will be affected is 100%. The probability that an autosomal recessive trait will be passed to the child of consanguineous parents is much higher than it is in non-consanguineous parents.

Sex-linked Mendelian inheritance

Sex-linked traits are carried on the X and Y, or sex, chromosomes. Sex-linked traits may be linked to either the X or the Y chromosome and may also be either dominant, semi-dominant, or recessive. Many more X-linked traits have been identified than Y-linked traits.

The sex chromosomes control the biological sex of an individual. Individuals with XY chromosomes are male, and individuals with XX chromosomes are female. The chromosome inherited from the mother is always the X chromosome, while the chromosome carried by the father's sperm may be either an X or Y chromosome.

X-LINKED DOMINANT Chromosomally normal females possess two X chromosomes; therefore, they can be homozygous or heterozygous in a trait that is caused by a **gene mutation** on the X chromosome. In the case of X-linked dominant traits, only one copy of the mutant gene must be present for the trait to be fully expressed. A female child affected with an X-linked trait may inherit this trait from either her mother or her father. In cases of

KEY TERMS

Allele—One of two or more alternate forms of a gene.

Anticipation—Increasing severity in disease with earlier ages of onset, in successive generations; a condition that begins at a younger age and is more severe with each generation.

Asymptomatic carrier—A person who carries a recessive trait but does not show any characteristics of the trait.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Candidate gene—A gene that encodes proteins believed to be involved in a particular disease process.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Consanguineous—Sharing a common bloodline or ancestor.

***de novo* mutation**—Genetic mutations that appear for the first time in an affected person. They result from errors in the DNA in the sperm or egg of the parents, not because of the occurrence of these same mutations within the typical chromosomes of one of the parents.

Dominant—A trait that is expressed equally in homozygous, heterozygous, and hemizygous individuals.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Genome—A term used to describe a complete representation of all of the genes in a species.

Hemizygous—Having only one copy of a gene or chromosome.

Heterozygous—Having two different versions of the same gene.

Homozygous—Having two identical copies of a gene or chromosome.

Loci—The physical location of a gene on a chromosome.

Male-lethal X-linked dominance—An inheritance pattern in which affected male children die from the characteristics of the trait. This death is typically either embryonic, fetal, or neonatal.

Mitochondrial inheritance—Inheritance associated with the mitochondrial genome which is inherited exclusively from the mother.

Mosaicism—A genetic condition resulting from a mutation, crossing over, or nondisjunction of chro-

(continued)

an affected heterozygous mother and an unaffected father, the probability that a female child will be affected with an X-linked dominant trait is 50%. In cases of an affected homozygous mother, the probability that a female child will be affected is 100%, regardless of whether or not the father is affected. In cases of an affected father, the probability that a female child will be affected is 100%. This is because the father is hemizygous for the mutant allele. His only copy is affected and he must pass that copy on to his daughters.

A chromosomally normal male child must receive his only X chromosome from his mother. He gets his Y chromosome from his father. Therefore, in cases of X-linked dominant traits, a male child has a 50% chance that he will receive the mutant gene from his heterozygous affected mother. If his mother is homozygous, this male child has a 100% likelihood of being affected with the trait. Therefore, while X-linked dominant traits are passed on equally from mothers to daughters and from mothers to sons, females may also inherit X-linked dominant traits from their fathers.

In some instances of dominant X-linked inheritance, the lack of the presence of a copy of the normal gene causes embryonic, fetal, or neonatal death. Therefore, in these cases, only very few affected males are born alive, and those that are generally die within a few hours of birth. This inheritance pattern is also known as male-lethal X-linked dominant inheritance. Since there are no affected males to contribute to the inheritance patterns of these traits, inheritance from father to daughter is not possible. Likewise, homozygous females are not possible. Only heterozygous females survive. In this form of inheritance, all affected males will inherit this trait from their heterozygous mothers. These males will either

KEY TERMS (CONTINUED)

mosomes during cell division, causing a variation in the number of chromosomes in the cells.

Nuclear inheritance—Inheritance associated with the nuclear genome (the 23 pairs of chromosomes). This inheritance follows the rules of segregation developed by Gregor Mendel and is alternately termed Mendelian inheritance.

Pedigree analysis—Analysis of a family tree, or pedigree, in an attempt to identify the possible inheritance pattern of a trait seen in this family.

Penetrance—The degree to which individuals possessing a particular genetic mutation express the trait that this mutation causes. One hundred percent penetrance is expected to be observed in truly dominant traits.

Phenotype—The physical expression of an individual's genes.

Polymorphism—A change in the base pair sequence of DNA that may or may not be associated with a disease.

Pseudodominant—A recessive trait that appears, in a pedigree analysis, to be a dominant trait.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

Semi-dominant—A trait expressed as a severe form in homozygous affected individuals and a milder form in heterozygous affected individuals.

Sex-linked—Related to either the X or the Y chromosome.

Symptomatic carrier—A heterozygous person who carries a semi-dominant trait. This person experiences milder characteristics of this trait than a person who is homozygous or hemizygous in this trait.

Trait—The set of physically observable characteristics that results from the expression of a gene.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

Variable expression—Instances in which an identical genetic mutation leads to varying traits from affected individual to affected individual. This variance may occur between members of two separately affected families or it may occur between affected members of the same family.

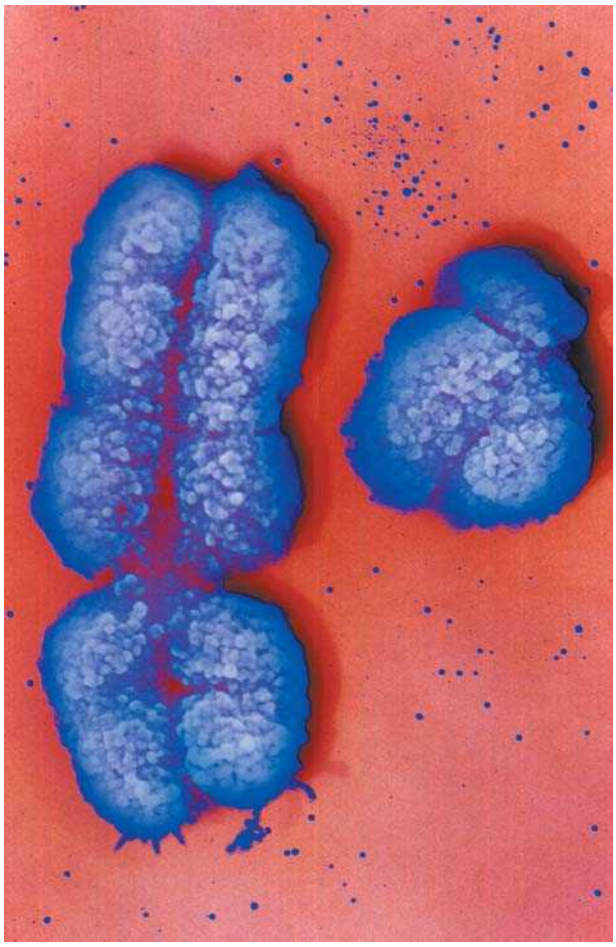
X chromosome—One of the two sex chromosomes (the other is Y) containing genetic material that, among other things, determine a person's gender.

X-inactivation—A condition in which one of the X chromosomes of a female is suppressed, or "turned off," in favor of the other X chromosome. Preferential X-inactivation is a process in which one X chromosome is inactivated in all the cells of the body, in preference to the other X chromosome. Females with preferential X-inactivation express X-linked traits as if they are hemizygous rather than homozygous or heterozygous.

become miscarriages, they will be stillborn, or they will die shortly after birth. Heterozygous females can inherit male-lethal X-linked dominant traits from their heterozygous mothers. Therefore, the inheritance of these traits has an overall 50% probability of occurrence.

X-LINKED RECESSIVE In cases of X-linked recessive traits, female children can only be affected if their mothers are carriers and their fathers are affected with the trait. The inheritance patterns in females of X-linked recessive traits are identical to the inheritance patterns of autosomal recessive traits. However, because the odds of a carrier mother producing offspring with an affected father are extremely low, X-linked recessive traits are characterized by the general absence of affected females. Because males are hemizygous in all X-linked traits, they have a 50% probability of inheriting an X-linked recessive trait from their carrier mothers. In the rare instances of affected mothers, males have a 100% chance of inheritance. Fathers cannot pass any X-linked trait to their XY sons. When affected fathers produce female children, 100% of these girls will be carriers of this trait. Almost all cases of females affected by an X-linked recessive trait are the result of consanguineous parents.

X-LINKED SEMI-DOMINANT A few examples of X-linked semi-dominant traits exist. In these cases, the carrier females are generally affected with a milder form of the trait than the affected males. Occasionally, some females show mosaicism of their X chromosomes that causes an activation of one of the X chromosomes in preference to the other. In these cases, heterozygous females show characteristics of the trait caused by the mutant gene that are identical, or nearly identical, to those characteristics seen in hemizygous affected males. Examples of this type of X-inactivation are a form of



A scanning electron micrograph (SEM) of the female X chromosome (left) and male Y chromosome (right). *(Photo Researchers, Inc.)*

hereditary mental retardation called **fragile X syndrome**, and both Duchenne type and Becker type muscular dystrophies.

Mitochondrial inheritance

A human being is conceived by the joining of the egg from the mother and the sperm from the father. Relative to the egg, the sperm is extremely small. It contains almost no cellular material outside the nucleus (cytoplasm) and very few mitochondria. In the cytoplasm of the egg, cellular components called mitochrondria are present. These mitochondria carry mitochondrial DNA, which is circular and contains 16,569 base pairs. Each mitochondrion contains between two and ten copies of this mitochondrial DNA. This separate genome codes for two ribosomal RNAs, 22 transfer RNAs, and 13 proteins that are used as enzymes in oxidative phosphorylation (cellular metabolism). Almost all the mitochondria in a person are derived from maternal mitochondria. Therefore, traits that result from mutations in mitochondrial DNA are exclusively inherited from the mother. These traits are not characterized by dominant, recessive, or semi-dominant patterns.

Most often, mitochondrial DNA is mosaic for a particular trait. That is to say, the trait exists on some, but not all, of the mitochondrial DNA in each cell. There can be as few as two or as many as ten copies of this mitochondrial DNA in a single cell. When cell division occurs, these mitochondrial DNA are randomly distributed into the newly formed mitochondria of the daughter cells. In most cases this mosaicism is such that only certain cells of the body contain the mutant DNA forms while other cells of the body are normal.

Human pedigree analysis

A **pedigree analysis** is the inspection of a family tree to look for the inheritance pattern of a trait associated with a mutant gene or a chromosomal aberration. Because the size of human families is usually quite small, it is often impossible to determine the inheritance pattern of a particular trait by performing a pedigree analysis on a single family. Other complications arise when analyzing human pedigrees. Among these are: anticipation; *de novo* mutations, improper identification of members of the pedigree; mosaicism; penetrance; variable expression; and recessive conditions appearing dominant, or pseudo-dominant.

Anticipation is the tendency of a trait to become more severely expressed in succeeding generations. This is called anticipation because the more severely affected child is discovered first, then other members of the pedigree are often "anticipated" as having to be affected with milder forms of that trait. While this anticipation was originally thought to be an error in backward identification of a trait in preceding generations caused by the identification of that trait in succeeding generations, it is now recognized as a true genetic characteristic. As an example, fragile X syndrome has been demonstrated to affect each succeeding generation more severely than the preceding generation within the same family.

De novo mutations, or mutations that were not inherited from either parent, can cloud the pedigree analysis within a family. The individual who is affected did not inherit these *de novo* mutations but he or she may pass them on to his or her children. In these cases, if the pedigree analysis does not span a significant number of generations after the *de novo* affected person, the true genetic inheritance pattern of this new trait may not be able to be identified. In such cases of a lack of succeeding generations, the cause can often be mislabeled as not of hereditary origin (sporadic).

Improper identification of members of the pedigree has to be avoided when performing a pedigree analysis. This occurs most often when the father of a particular child is misidentified.

Mosaicism often causes traits to appear to have a dominant inheritance pattern in some families while that same trait appears to be recessive in other families.

Penetrance is the term used to describe the probability that a person possessing a genetic mutation will express that mutation. A true dominant trait will have a penetrance of 100%. However, many traits that are termed dominant do not have complete penetrance. Therefore, some individuals with an otherwise dominant seeming trait may be asymptomatic for that trait. Penetrance is often also problematic in age-related traits. In these traits, a dominant inheritance pattern may be missed because members of the pedigree died of causes unrelated to the dominant trait prior to developing symptoms of the trait.

Variable expression is extremely common in dominant traits. In these cases, identical mutant alleles cause different characteristics of expression in different people. This may be a variance of symptoms from one affected family to another affected family or it may be a variance of symptoms from one individual to another within a single family.

Recessive traits may appear to be dominant, or pseudo-dominant, within a pedigree. If a particular trait has a high frequency in the population, it is likely that two or more people may have independently introduced this trait into a single pedigree. This is in contrast to the typical founder effect, in which a single "founder" individual introduces the trait into the pedigree. A "founder" may be a person who is affected with a *de novo* mutation that enters the pedigree with them. Or, it may be a person who comes from a relatively separate **gene pool**, such as a European explorer entering the formerly isolated gene pool of a remote tribe or race of people.

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Paul A. Johnson

Ivemark syndrome *see* **Asplenia**

J

Jackson-Weiss syndrome

Definition

Jackson-Weiss syndrome (JWS) is a hereditary disease of varying severity affecting the skull, the face, and the feet. JWS is inherited in an autosomal dominant manner.

Description

Jackson-Weiss syndrome is characterized by a small midface, unusual skull shape, and foot abnormalities. The feet display very wide big toes and webbing of the skin between the second and third toes. Additionally, the toes are angled inward. Bony foot defects apparent on x ray include short, wide foot bones and fusion of some of the foot and ankle bones.

The hallmark skull differences associated with JWS are caused by the premature closure of skull sutures, or skull plates. Other features include a small jaw, flattening of the nasal bridge and the middle third of the face, and a beaked nose. The eyes may be crossed and are widely set and slanting downward with droopy eyelids. High arching of the roof of the mouth or cleft palate, an incomplete closure of the roof of the mouth, may also be present. Mental retardation has been reported in some individuals with JWS.

Genetic profile

Jackson-Weiss syndrome is inherited in an autosomal dominant manner. This means that possession of only one copy of the defective **gene** is enough to cause disease. When a parent has Jackson-Weiss syndrome each of his or her children have a 50% chance to inherit the disease-causing mutation. JWS is believed to have a high rate of penetrance. This means that almost all people who inherit the altered gene will manifest symptoms. JWS has also occurred spontaneously in babies with no family history of it or any similar disorder. This is known as a sporadic occurrence.

JWS has been associated with changes in two different fibroblast growth factor receptor genes, the FGFR1 and FGFR2 genes. The fibroblast growth factor receptor genes serve as a blueprint for proteins important in inhibiting growth during and after embryonic development. FGFR1 is located on human chromosome 8 in an area designated as 8p11.2-p11.1. FGFR2 is located on human chromosome 10 in an area designated as 10q26.

As of 2001, FGFR1 has been associated with JWS in only one reported patient who had an unusual presentation of the disorder. This patient displayed JWS's characteristic toes, foot bone fusion, and short fingers, but only very mild skull and facial differences. The genetic change seen in this patient had been seen before in a patient with symptoms much like **Pfeiffer syndrome**, another inherited disorder that affects the skull, face, and hands.

Most commonly, JWS is associated with changes in FGFR2. Mutations in FGFR2 are also associated with the more common **Crouzon syndrome**, a similar inherited disease that affects the skull and face. As of 2001 it appears that the same mutations can be associated with different diseases. Some families, like the original Amish family diagnosed with Jackson-Weiss syndrome, have members who may appear to have Crouzon syndrome or Pfeiffer syndrome. The family as a whole, however, was diagnosed as having Jackson-Weiss syndrome. In 1996, two scientists proposed that the name Jackson-Weiss syndrome should strictly be used in families like the original JWS family where different family members display features of more than one of these similar disorders (Crouzon, Pfeiffer, and **Apert syndromes**). As of 2001, there is controversy regarding this suggestion.

Demographics

JWS has been described in different races and geographic regions. The original Jackson-Weiss family was a large Amish family with at least 138 affected members. JWS affects both sexes equally. The strongest risk factor

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

for JWS is a family history of the disorder. As of 2001, no precise estimates on the frequency of JWS are available.

Signs and symptoms

Jackson-Weiss syndrome's hallmarks are variable skull differences, flattened mid-face, and wide big toes that angle inward toward each other. The hands are usually not involved. Rarely, deafness or mental retardation can be seen in people with JWS.

Skull abnormalities vary between individuals. Abnormalities in skull shape happen when the sutures, or open seams between the bony plates that form the skull, fuse before they normally would. Premature closure of the skull sutures is known as **craniosynostosis**. Growth of the brain pushes outward on skull plates that have not yet fused. In JWS different sutures may be involved leading to different head shapes. The face may be lopsided due to skull deformity.

Facial differences also vary between individuals with Jackson-Weiss syndrome. Some individuals have no obvious facial differences. The hallmark face of Jackson-Weiss syndrome has very prominent, bulging, down slanting, sometimes crossed eyes that are slightly further apart than normal with droopy eyelids. The middle third of the face is underdeveloped and somewhat flattened with a beaked nose. The forehead is rounded prominently and the hairline may be slightly lower on the forehead than usual. The chin may be small and the lower jaw may come forward more than normal. Some people with JWS may have cleft palate or a steeply arched palate (roof of the mouth). These changes may cause unusually nasal sounding speech or more serious speech difficulties.

The feet display unusually wide big toes that curve inward toward each other. The large bones of the foot may be fused or abnormally shaped. Smaller bones of the feet and toes may be abnormally shaped or absent. These bony abnormalities may be obvious only on x ray. The fingers and toes may be abnormally short with webbing of the skin between the second and third toes. Extra toes may be present at birth.

Diagnosis

Characteristic facial features and unusual toes may be obvious to an untrained eye, but a thorough physical exam by a physician is necessary to check for less obvious differences. Bony differences may not be obvious, appearing only on x ray. Bony differences in the feet were found consistently, even in seemingly unaffected individuals, in the original Jackson-Weiss syndrome family. X ray is considered to be a very important element in diagnosing JWS. X rays are also important in determining what specific type of abnormal skull plate fusion is present.

DNA testing is available for Jackson-Weiss syndrome. This testing is performed on a blood sample in children and adults to confirm a diagnosis made on physical features. Prenatal **genetic testing** is also available. An unborn baby can be tested for JWS with **DNA** extracted from cells obtained via chorionic villus sampling or **amniocentesis**.

Treatment and management

There is no medication or cure for Jackson-Weiss syndrome. Treatment, if necessary, depends on an individual's symptoms. Surgery is always offered to correct the most severe physical complications, like cleft palate. Foot and facial abnormalities can also be treated with surgery if they are bothersome to an affected individual. Cosmetic surgery on the face can yield excellent results. In many cases facial differences are so mild that surgical intervention is not recommended. Counseling and support groups may be helpful to patients experiencing emotional difficulty due to physical differences.

Genetic counseling is offered to persons who have this inheritable disorder. Parents with this disease have a

50% chance of passing it to each of their children. Prenatal diagnosis for JWS is available. This prenatal genetic testing cannot, however, predict the severity or scope of an individual's symptoms. In the future, parents with genetic diseases like Jackson-Weiss syndrome may be able to opt for disease diagnosis from a cell of an embryo before the embryo is introduced to the mother's womb. This testing is called preimplantation genetic diagnosis and is already available in some centers in the United States.

Prognosis

The lifespan of individuals with JWS is normal. Intelligence is often normal, though borderline intelligence and mental retardation have been described in some patients with JWS.

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Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

FACES. The National Craniofacial Assocation. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

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Judy C. Hawkins, MS

Jacobsen syndrome

Definition

Jacobsen syndrome is a rare chromosome disorder that affects multiple aspects of physical and mental development.

Description

Jacobsen syndrome is characterized by a distinctive facial appearance, some degree of mental impairment, and certain types of birth defects, especially of the heart. Other common medical complications include recurrent infections, decreased platelet count, failure to thrive, and slow growth. The syndrome derives its name from a Danish physician, Dr. Petra Jacobsen, who first described an affected child in 1973. It is also known as 11q deletion syndrome or partial 11q monosomy syndrome because a specific region of one copy of chromosome 11 is missing and thus an affected person has one out of a possible two copies of the genes in that region. It is the loss of these genes that leads to the multiple problems found in Jacobsen syndrome.

Genetic profile

The loss of genetic material from a specific segment of chromosome 11q, which at least includes the critical region at band 11q24.1, leads to the manifestations of Jacobsen syndrome. There are several ways in which this portion of chromosome 11 can be deleted. In at least two-thirds of Jacobsen syndrome cases there is a partial chromosome 11q deletion (a terminal deletion) that begins at band q23 and extends through the end of the chromosome. The remainder of cases are attributed to the loss of this chromosome 11q genetic material due a deletion within, but not including, the end of the chromosome (an interstitial deletion), or due to a chromosome rearrangement such as an unbalanced chromosome translocation or a ring chromosome.

Most deletions and chromosome rearrangements responsible for Jacobsen syndrome are not familial; they are the result of a new or *de novo* genetic change that occurred only in the gamete (the egg or sperm) contributed by the mother or father of that individual. Less often, the origin of chromosome deletion or rearrangement is familial. In a minority of cases a parent of an affected child has a folate-sensitive fragile site at chromosome band 11q23.3 that can cause chromosomal breakage and subsequent deletion of chromosome 11q when inherited. Also, there are children who have inherited an unbalanced chromosome translocation from a parent who is a balanced translocation carrier.

Demographics

Although it is not known how many people have Jacobsen syndrome, estimates are that one person in every 100,000 is affected by the disorder. More females than males have the disorder with 70–75% of cases being females.

Signs and symptoms

Symptoms of Jacobsen syndrome are variable and the prognosis for an affected child depends on the presence of life-threatening birth defects or medical problems. Individuals with Jacobsen syndrome have a distinctive physical appearance. The face is characterized by wide-spaced eyes (hypertelorism), droopy eyelids (ptosis), redundant skin covering the inner eye (epicanthal folds), a broad or flat nasal bridge, a short nose with upturned nostrils, a small chin (micrognathia), low-set ears, and a thin upper lip. As many as 90–95% of affected individuals have a malformation of the skull, trigonocephaly, a defect that results from premature closure of one of the cranial sutures. A small head size (microcephaly) is found in over one-third of cases. Overall, individuals with Jacobsen syndrome are smaller than their peers or siblings. Prenatal growth retardation occurs about 75% of the time. A newborn with Jacobsen syndrome is usually small at birth and continues to have delayed growth and subsequent short stature. Feeding problems that can result in failure to thrive are also common.

Children with Jacobsen syndrome usually have some degree of developmental delay or mental retardation, ranging from mild to severe. Nearly all affected individuals also have decreased muscle tone (hypotonia) or increased muscle tone (hypertonia) as well as fine and gross motor delays. Occasionally, brain abnormalities are present.

Multiple types of physical abnormalities are known to occur in individuals with Jacobsen syndrome. Congenital heart disease is present in about half of affected children and, if severe, can pose a significant health problem. Other common internal abnormalities include **pyloric stenosis**, undescended testes, inguinal hernia, kidney defects, and urinary tract abnormalities. Craniofacial abnormalities such as strabismus, ptosis, colobomas, a high-arched palate, and external ear anomalies are frequent. Orthopedic problems, mainly joint contractures and abnormalities of the digits (the fingers and toes), have been described in some cases.

In addition to congenital defects, there are a variety of other health problems found in individuals with Jacobsen syndrome. Illnesses including recurrent respiratory infections, sinusitis, and otitis media occur more frequently in children with Jacobsen syndrome. Gastrointestinal problems such as gastroesophageal reflux and chronic constipation may occur. Blood disorders such as thrombocytopenia and pancytopenia are often seen in childhood and may improve with time.

Diagnosis

Most individuals with Jacobsen syndrome are diagnosed after birth. The diagnosis is usually made through a blood test called chromosome analysis in an infant or child who has mental retardation and a typical facial appearance. The **karyotype** will show a deletion or rearrangement of the longer segment, known as the q arm, of one copy of chromosome 11. Jacobsen syndrome can be diagnosed before birth. There have been reports of prenatal diagnosis through **amniocentesis** after an ultrasound demonstrated one or more fetal abnormalities. Another technique, known as FISH (fluorescent in-situ hybridization), may be used to further define the chromosome 11q deletion breakpoints; this laboratory test is being done on a research basis to identify the disease-causing genes in the Jacobsen syndrome critical region.

Treatment and management

There is no cure for Jacobsen syndrome nor is there a therapy that can replace the missing genes from the deleted segment of chromosome 11. In addition to routine pediatric exams, there are management strategies and treatments that aim to prevent or minimize some of the serious health consequences associated with Jacobsen syndrome.

At the time of diagnosis a series of evaluations should be undertaken in order to appropriately guide medical management. Pediatric specialists in genetics, cardiology, orthopedics, ophthalmology, and neurology should be consulted, especially since some problems can be treated if caught early. Important tests may include a karyotype, a cardiac echocardiogram, a renal sonogram, a platelet count, a blood count, a brain imaging study, hearing and vision screenings, and a dental exam.

A neurodevelopmental evaluation should be initiated in infancy or at the time of diagnosis with implementation of age-appropriate early intervention services such as speech therapy, occupational therapy, and physical therapy. An ear, nose, and throat specialist (ENT) may be needed to treat problems such as otitis media. Craniofacial and neurosurgery consults may be indicated if trigonocephaly or other forms of **craniosynostosis** are present.

Some children may require a gastroenterology specialist to evaluate problems such as failure to thrive, chronic constipation, and/or severe gastroesophageal reflux, some or all of which may require surgical intervention. Boys with Jacobsen syndrome should be examined for undescended testes, a problem found in half of males and one that often requires surgery.

Prognosis

Approximately 25% of affected children die before two years of age mainly from cardiac defects, a tendency to bleed, or infection. Except for respiratory infections, the remainder of children are generally healthy. Most individuals described here are children or adolescents. Little is known about the course of this syndrome in adulthood, and the life expectancy for those who live beyond age two is unknown.

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Dawn Cardeiro, MS, CGC

Jervell and Lange-Nielsen syndrome

Definition

Jervell and Lange-Nielsen syndrome (JLNS) is a rare inherited disorder characterized by congenital deafness and cardiac arrhythmias (irregularities in the electrical activity of the heart that can lead to cardiac arrest and sudden death).

Description

JLNS results from mutations, or changes, in either one of two genes that encode proteins that combine to form potassium ion channels. One of the potassium channels is important for proper heart function. It is also critical in the functioning of the cochlea of the inner ear. People with JLNS lack this channel and, thus, are born with profound deafness in both ears, as well as with cardiac abnormalities.

JLNS was first described in 1957 by A. Jervell and F. Lange-Nielsen. It is also known by the names cardioauditory syndrome of Jervell and Lange-Nielsen; cardiocardiac syndrome; surdocardiac syndrome; deafness-functional heart disease; and deafness, congenital, and functional heart disease. The cardiac (heart) symptoms of JLNS are very similar to those of **long-QT syndrome** (LQTS), including a longer-than-normal "QT interval" on an electrocardiogram (ECG or EKG) test. Thus, JLNS is sometimes called QT prolonged with congenital deafness.

Genetic profile

JLNS is caused by mutations in either the KVLQT1 (KCNQ1) **gene** or the KCNE1 (MinK or IsK) gene. It is an autosomal recessive disorder, which means it occurs only in people with two copies of the mutant gene, one from each parent. The mutations in the two copies do not have to be identical. Someone who inherits one copy of the mutant gene and one copy of the normal gene has LQTS types 1 or 5.

Demographics

Although it is the third most common type of autosomal recessive hearing loss, JLNS is a very rare disorder. Worldwide, there are an estimated two to six cases per one million people. Norway, however, has a much higher incidence of JLNS, estimated at one in 200,000.

Because JLNS requires two copies of the abnormal gene, one from each parent, it most often is found in the offspring of related parents, such as cousins (termed a "consanguineous" marriage). Individuals who carry one copy of the abnormal gene and one normal gene copy will have LQTS, but will have normal hearing or only partial hearing loss. However, a child of two such individuals has a 25% chance of having JLNS. Thus, although JLNS occurs across racial and ethnic groups, it is more common in small isolated groups where marriage between relatives is frequent.

KEY TERMS

Action potential—The wave-like change in the electrical properties of a cell membrane, resulting from the difference in electrical charge between the inside and outside of the membrane.

Arrhythmia—Abnormal heart rhythm, examples are a slow, fast, or irregular heart rate.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Beta-adrenergic blocker—A drug that works by controlling the nerve impulses along specific nerve pathways.

Cochlea—A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

Congenital—Refers to a disorder which is present at birth.

Depolarization—The dissipation of an electrical charge through a membrane.

Electrocardiogram (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Endolymph—The fluid in the inner ear.

Fibrillation—A rapid, irregular heartbeat.

Heterozygous—Having two different versions of the same gene.

Homeostasis—A state of physiological balance.

Homozygous—Having two identical copies of a gene or chromosome.

Ion channel—Cell membrane proteins which control the movement of ions into and out of a cell.

QT interval—The section on an electrocardiogram between the start of the QRS complex and the end of the T wave, representing the firing or depolarization of the ventricles and the period of recovery prior to repolarization or recharging for the next contraction.

Repolarization—Period when the heart cells are at rest, preparing for the next wave of electrical current (depolarization).

Syncope—A brief loss of consciousness caused by insufficient blood flow to the brain.

Tachycardia—An excessively rapid heartbeat; a heart rate above 100 beats per minute.

Torsade de pointes—A type of tachycardia of the ventricles characteristic of Jervell and Lange-Nielsen syndrome.

Signs and symptoms

The deafness associated with JLNS usually is apparent in infancy or early childhood. Although the severity of JLNS varies, children with acute JLNS are profoundly deaf in both ears.

Depending on the severity of the disorder, the cardiac symptoms of JLNS may be overlooked. Thus, people with JLNS can be at serious risk for sudden death. In addition to a prolonged QT interval on an ECG/EKG, cardiac arrhythmias, dizziness, periods of unconsciousness (syncopic episodes), and seizures are common symptoms of JLNS. These symptoms most often occur upon awakening, during strenuous physical activity, or during moments of excitement or stress.

Diagnosis

Deaf children, particularly those with a family history of sudden death, syncopic episodes, or LQTS should be screened for JLNS, using an ECG to detect a prolonged QT interval. **Genetic testing** for JLNS is possible for high-risk individuals.

Individuals with JLNS sometimes have normal or borderline-normal QT intervals on an ECG/EKG. Additional ECGs/EKGs performed during exercise may reveal an abnormal QT interval. ECGs/EKGs of the parents may also reveal a prolonged QT interval.

Treatment and management

Since JLNS can result in sudden death, including sudden infant death syndrome (SIDS), treatment is essential. Beta-blockers are the most common treatment for the ventricular arrhythmia of JLNS. Treatment with these drugs usually continues for life. Beta-blockers such as propranolol are considered to be safe medications. Any side effects from propranolol are usually mild and disappear once the body has adjusted to the drug. However, beta-blockers can interact dangerously with many other medications.

Surgery may reduce cardiac arrhythmias in people with JLNS. A mechanical device called a pacemaker or an automatic implanted cardioverter defibrillator (AICD) may be used to regulate the heartbeat or to detect and correct abnormal heart rhythms. Sometimes a pacemaker or AICD is used in combination with beta-blockers.

In 2000, the first cochlear implant in the inner ear of a child with JLNS was reported. The child gained limited hearing and improved speech.

Preventative measures

All individuals who have been diagnosed with JLNS must avoid reductions in blood potassium levels, such as those that occur with the use of diuretics (drugs that reduce fluids in the body). People with JLNS must also avoid a very long list of drugs and medications that can increase the QT interval or otherwise exacerbate the syndrome.

People with JLNS usually are advised to refrain from competitive sports and to practice a "buddy system" during moderate exercise. Family members are advised to learn cardiopulmonary resuscitation (CPR) in case of cardiac arrest.

Prognosis

Cochlear implants may improve the hearing of people with JLNS. The cardiac abnormalities of JLNS usually can be controlled with beta-blockers. However, without treatment, there is a high incidence of sudden death due to cardiac events.

Family members of a JLNS individual should be screened with ECGs/EKGs for a prolonged QT interval, since they are at risk of having LQTS. **Genetic counseling** is recommended for people with JLNS, since their children will inherit a gene causing LQTS.

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ORGANIZATIONS

American Heart Association. 7272 Greenville Ave., Dallas, TX 75231-4596. (214) 373-6300 or (800) 242-8721. inquire @heart.org. <http://www.americanheart.org>.

American Society for Deaf Children. PO Box 3355, Gettysburg, PA 17325. (800) 942-ASDC or (717) 334-7922 v/tty. <http://www.deafchildren.org/asdc2k/home/home.shtml>.

Deafness Research Foundation. 575 Fifth Ave., 11th Floor, New York, NY 10017. (800) 535-3323. drf@drf.org.

EAR (Education and Auditory Research) Foundation. 1817 Patterson St., Nashville, TN 37203. (800) 545-HEAR. earfound@earfoundation.org. <http://www.theearfound.org>.

European Long QT Syndrome Information Center. Ronnerweg 2, Nidau, 2560. Switzerland 04(132) 331-5835. jmettler@bielnews.ch. <http://www.bielnews.ch/cyberhouse/qt/qt.html>.

Sudden Arrhythmia Death Syndrome Foundation. PO Box 58767, 508 East South Temple, Suite 20, Salt Lake City, UT 84102. (800) 786-7723. sads@sads.org. <http://www.sads.org>.

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Margaret Alic, PhD

Joubert syndrome

Definition

Joubert syndrome is a well documented but rare autosomal recessive disorder. The syndrome is characterized by partial or complete absence of the cerebellar vermis (the connective tissue between the two brain hemisperes), causing irregular breathing and severe muscle weakness. Other features of the syndrome include jerky eye movements, abnormal balance and walking, and mental handicap. There may be minor birth defects of the face, hands, and feet.

Description

Marie Joubert (whose name is given to the condition) gave a detailed description of the syndrome in 1969. She wrote about four siblings (three brothers, one sister) in one family with abnormal breathing, jerky eye movements (nystagmus), poor mental development, and ataxia

(staggering gait and imbalance). X ray examination showed that a particular section of the brain, called the cerebellar vermis, was absent or not fully formed. This specific brain defect was confirmed on autopsy in one of these individuals. Her initial report also described a sporadic (non-inherited) patient with similar findings, in addition to polydactyly. Another name for Joubert syndrome is Joubert-Bolthauser syndrome.

Genetic profile

There have been numerous instances of siblings (brothers and sisters), each with Joubert syndrome. The parents were normal. A few families have also been seen where the parents were said to be closely related (i.e. may have shared the same altered **gene** within the family). For these reasons, Joubert syndrome is an autosomal recessive disorder. Autosomal means that both males and females can have the condition. Recessive means that both parents would be carriers of a single copy of the responsible gene. Autosomal recessive disorders occur when a person inherits a particular pair of genes that do not work correctly. The chance that this would happen to children of carrier parents is 25% (1 in 4) for each pregnancy.

It is known that the cerebellum and brain stem begin to form between the sixth and twelfth week of pregnancy. The birth defects seen in Joubert syndrome must occur during this crucial period of development. As of 2001, the genetic cause remains unknown.

Demographics

Joubert syndrome affects both males and females, although more males (ratio of 2:1) have been reported with the condition. The reason why more males have the condition remains unknown.

Joubert syndrome is found worldwide, with reports of individuals of French Canadian, Swedish, German, Swiss, Spanish, Dutch, Italian, Indian, Belgian, Laotian, Moroccan, Algerian, Turkish, Japanese, and Portuguese origin. In all, more than 200 individuals have been described with Joubert syndrome.

Signs and symptoms

The cerebellum is the second largest part of the brain. It is located just below the cerebrum, and partially covered by it. The cerebellum consists of two hemispheres, separated by a central section called the vermis. The cerebellum is connected to the spinal cord, through the brain stem.

The cerebellum (and vermis) normally works to monitor and control movement of the limbs, trunk, head, and eyes. Signals are constantly received from the eyes, ears, muscle, joints, and tendons. Using these signals, the cerebellum is able to compare what movement is actually happening in the body, with what is intended to happen. Then, it sends an appropriate signal back. The effect is to either increase or decrease the function of different muscle groups, to make movement both accurate and smooth.

In Joubert syndrome, the cerebellar vermis is either absent or incompletely formed. The brain stem is sometimes quite small. The absence or abnormal function of these brain tissues causes problems in breathing and vision, and severe delays in development.

One characteristic feature of Joubert syndrome is the pattern of irregular breathing. Their breathing alternates between deep rapid breathing (almost like panting) with periods of severe apnea (loss of breathing). This is usually noticeable at birth. The rate of respira-

KEY TERMS

Apnea—An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Cerebellum—A portion of the brain consisting of two cerebellar hemispheres connected by a narrow vermis. The cerebellum is involved in control of skeletal muscles and plays an important role in the coordination of voluntary muscle movement. It interrelates with other areas of the brain to facilitate a variety of movements, including maintaining proper posture and balance, walking, running, and fine motor skills, such as writing, dressing, and eating.

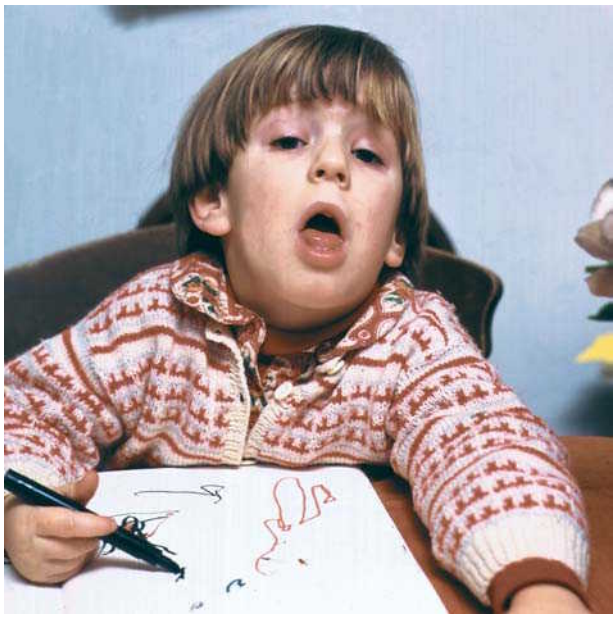
Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Nystagmus—Involuntary, rhythmic movement of the eye.

Polydactyly—The presence of extra fingers or toes.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Vermis—The central portion of the cerebellum, which divides the two hemispheres. It functions to monitor and control movement of the limbs, trunk, head, and eyes.



This child is diagnosed with Joubert syndrome. Common symptoms of this disorder include mental retardation, poor coordination, pendular eye movement, and abnormal breathing patterns. *(Photo Researchers, Inc.)*

tion may increase more than three times that of normal (up to 200 breaths per minute) and the apnea may last up to 90 seconds. The rapid breathing occurs most often when the infant is awake, especially when they are aroused or excited. The apnea happens when the infants are awake or asleep. Such abnormal breathing can cause sudden death or coma, and requires that these infants be under intensive care. For unknown reasons, the breathing tends to improve with age, usually within the first year of life.

Muscle movement of the eye is also affected in Joubert syndrome. It is common for the eyes to have a quick, jerky motion of the pupil, known as nystagmus. The retina (the tissue in the back of the eye that receives and transmits visual signals to the brain) may be abnormal. Some individuals (most often the males) may have a split in the tissue in the iris of the eye. Each of these problems will affect their vision, and eye surgery may not be beneficial.

The central nervous system problem affects the larger muscles of the body as well, such as those for the arms and legs. Many of the infants will have severe muscle weakness and delays in development. They reach normal developmental milestones, such as sitting or walking, much later than normal. For example, some may learn to sit without support by around 19–20 months of age (normal is six to eight months). Most individuals are not able to take their first steps until age four or older. Their balance and coordination are also affected, which makes walking difficult. Many will have an unsteady gait, and find it difficult to climb stairs or run, even as they get older.

Cognitive (mental) delays are also a part of the syndrome, although this can be variable. Most individuals with Joubert syndrome will have fairly significant learning impairment. Some individuals will have little or no speech. Others are able to learn words, and can talk with the aid of speech therapy. They do tend to have pleasant and sociable personalities, but problems in behavior can occur. These problems most often are in temperament, hyperactivity, and aggressiveness.

Careful examination of the face, especially in infancy, shows a characteristic appearance. They tend to have a large head, and a prominent forehead. The eyebrows look high, and rounded, and the upper eyelids may be droopy (ptosis). Their mouth many times remains open, and looks oval shaped in appearance. The tongue may protrude out of the mouth, and rest on the lower lip. The tongue may also quiver slightly. These are all signs of the underlying brain abnormality and muscle weakness. Occasionally, the ears look low set on the face. As they get older, the features of the face become less noticeable.

Less common features of the syndrome include minor birth defects of the hands and feet. Some individuals with Joubert syndrome have extra fingers on each hand. The extra finger is usually on the pinky finger side (polydactyly). It may or may not include bone, and could just be a skin tag. A few of these patients will also have extra toes on their feet.

Diagnosis

The diagnosis of Joubert syndrome is made on the following features. First, there must be evidence of the cerebellar vermis either being absent or incompletely formed. This can be seen with a CT scan or MRI of the brain. Second, the physician should recognize the infant has both muscle weakness and delays in development. In addition, there may be irregular breathing and abnormal eye movements. Having four of these five criteria is enough to make the diagnosis of Joubert syndrome. Most individuals are diagnosed by one to three years of age.

Treatment and management

During the first year of life, many of these infants require a respiratory monitor for the irregular breathing. For the physical and mental delays, it becomes necessary

to provide special assistance and anticipatory guidance. Speech, physical, and occupational therapy are needed throughout life.

Prognosis

The unusual pattern of breathing as newborns, especially the episodes of apnea, can lead to sudden death or coma. A number of individuals with Joubert syndrome have died in the first three years of life. For most individuals, the irregular breathing becomes more normal after the first year. However, many continue to have apnea, and require medical care throughout their life. Although the true lifespan remains unknown, there are some individuals with Joubert syndrome who are in their 30s.

Resources

ORGANIZATIONS

Joubert Syndrome Foundation Corporation. c/o Stephanie Frazer, 384 Devon Drive, Mandeville, LA 70448.

OTHER

Alliance of Genetic Support Groups. <http://www.geneticalliance.org.htm>.

Joubert Syndrome Foundation Corporation. <http://www.joubertfoundation.com>.

Kevin M. Sweet, MS, CGC

K

Kabuki syndrome

Definition

Kabuki syndrome is a rare disorder characterized by unusual facial features, skeletal abnormalities, and intellectual impairment. Abnormalities in different organ systems can also be present, but vary from individual to individual. There is no cure for Kabuki syndrome, and treatment centers on the specific abnormalities, as well as on strategies to improve the overall functioning and quality of life of the affected person.

Description

Kabuki syndrome is a rare disorder characterized by mental retardation, short stature, unusual facial features, abnormalities of the skeleton and unusual skin ridge patterns on the fingers, toes, palms of the hands and soles of the feet. Many other organ systems can be involved in the syndrome, displaying a wide variety of abnormalities. Thus, the manifestations of Kabuki syndrome can vary widely among different individuals.

Kabuki syndrome (also known as Niikawa-Kuroki syndrome) was first described in 1980 by Dr. N. Niikawa and Dr. Y. Kuroki of Japan. The disorder gets its name from the characteristic long eyelid fissures with eversion of the lower eyelids that is similar to the make-up of actors of Kabuki, a traditional Japanese theatrical form. Kabuki syndrome was originally known as Kabuki Make-up syndrome, but the term “make-up” is now often dropped as it is considered offensive to some families.

Scientific research conducted over the past two decades suggests that Kabuki syndrome may be associated with a change in the genetic material. However, it is still not known precisely what this genetic change may be and how this change in the genetic material alters growth and development in the womb to cause Kabuki syndrome.

Genetic profile

As stated above, the etiology of Kabuki syndrome is not completely understood. While Kabuki syndrome is thought to be a genetic syndrome, little or no genetic abnormality has been identified as of yet. Chromosome abnormalities of the X and Y chromosome or chromosome 4 have occurred in only a small number of individuals with Kabuki syndrome, but in most cases, **chromosomes** are normal.

In almost all cases of Kabuki syndrome, there is no family history of the disease. These cases are thought to represent new genetic changes that occur randomly and with no apparent cause and are termed sporadic. However, in several cases the syndrome appears to be inherited from a parent, supporting a role for genetics in the cause of Kabuki syndrome. Scientists hypothesize that an unidentified genetic abnormality that causes Kabuki syndrome is transmitted as an autosomal dominant trait. With an autosomal dominant trait, only one abnormal **gene** in a gene pair is necessary to display the disease, and an affected individual has a 50% chance of transmitting the gene and the disease to a child.

Demographics

Kabuki syndrome is a rare disorder with less than 200 known cases worldwide, but the prevalence of the disease may be underestimated as only a handful of physicians have first-hand experience diagnosing children with Kabuki syndrome. Kabuki syndrome appears to be found equally in males and females. Earlier cases were reported in Japanese children but the syndrome is now known to affect other racial and ethnic groups.

Theoretical mathematical models predict that the incidence of Kabuki syndrome in the Japanese population may be as high as one in 32,000.

Signs and symptoms

The signs and symptoms associated with Kabuki syndrome are divided into cardinal symptoms (i.e. those

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Cardinal symptoms—A group of symptoms that define a disorder or disease.

Gastric tube—A tube that is surgically placed though the skin of the abdomen to the stomach so that feeding with nutritional liquid mixtures can be accomplished.

Gastroenterologist—A physician who specializes in disorders of the digestive system.

Kabuki—Traditional Japanese popular drama performed with highly stylized singing and dancing using special makeup and cultural clothing.

Neurologist—A physician who specializes in disorders of the nervous system, including the brain, spine, and nerves.

that are almost always present) and variable symptoms (those that may or may not be present). The cardinal and variable signs and symptoms of Kabuki syndrome are summarized in the table below.

Diagnosis

The diagnosis of Kabuki syndrome relies on physical exam by a physician familiar with the condition and by radiographic evaluation, such as the use of x rays or ultrasound to define abnormal or missing structures that are consistent with the criteria for the condition (as described above). A person can be diagnosed with Kabuki syndrome if they possess characteristics consistent with the five different groups of cardinal symptoms: typical face, skin-surface abnormalities, skeletal abnormalities, mild to moderate mental retardation, and short stature.

Although a diagnosis may be made as a newborn, most often the features do not become fully evident until early childhood. There is no laboratory blood or genetic test that can be used to identify people with Kabuki syndrome.

Treatment and management

There is no cure for Kabuki syndrome. Treatment of the syndrome is variable and centers on correcting the different manifestations of the condition and on strategies to improve the overall functioning and quality of life of the affected individual.

For children with heart defects, surgical repair is often necessary. This may take place shortly after birth if the heart abnormality is life threatening, but often physicians will prefer to attempt a repair once the child has grown older and the heart is more mature. For children who experience seizures, lifelong treatment with anti-seizure medications is often necessary.

Children with Kabuki syndrome often have difficulties feeding, either because of mouth abnormalities or because of poor digestion. In some cases, a tube that enters into the stomach, is placed surgically in the abdomen and specially designed nutritional liquids are administered through the tube directly into the stomach.

People with Kabuki syndrome are at higher risk for a variety of infections, most often involving the ears and the lungs. In cases such as these, antibiotics are given to treat the infection, and occasionally brief hospital stays are necessary. Most children recover from these infections with proper treatment.

Nearly half of people affected by Kabuki syndrome have some degree of hearing loss. In these individuals, formal hearing testing is recommended to determine if they might benefit from a hearing-aid device. A hearing aid is a small mechanical device that sits behind the ear and amplifies sound into the ear of the affected individual. Occasionally, hearing loss in individuals with Kabuki syndrome is severe, approaching total hearing loss. In these cases, early and formal education using American Sign Language as well as involvement with the hearing-impaired community, schools, and enrichment programs is appropriate.

Children with Kabuki syndrome should be seen regularly by a team of health care professionals, including a primary care provider, medical geneticist familiar with the condition, gastroenterologist, and neurologist. After growth development is advanced enough (usually late adolescence or early adulthood), consultation with a reconstructive surgeon may be of use to repair physical abnormalities that are particularly debilitating.

During early development and progressing into young adulthood, children with Kabuki syndrome should be educated and trained in behavioral and mechanical methods to adapt to any disabilities. This program is usually initiated and overseen by a team of health care professionals including a pediatrician, physical therapist, and occupational therapist. A counselor specially trained to deal with issues of disabilities in children is often helpful is assessing problem areas and encouraging healthy development of self-esteem. Support groups and community organizations for people with disabilities often prove useful to the affected individuals and their families, and specially equipped

enrichment programs should be sought. Further, because many children with Kabuki syndrome have poor speech development, a consultation and regular session with a speech therapist is appropriate.

Prognosis

The abilities of children with Kabuki syndrome vary greatly. Most children with the condition have a mild to moderate intellectual impairment. Some children will be able to follow a regular education curriculum, while others will require adaptations or modifications to their schoolwork. Many older children may learn to read at a functional level.

The prognosis of children with Kabuki syndrome depends on the severity of the symptoms and the extent to which the appropriate treatments are available. Most of the medical issues regarding heart, kidney or intestinal abnormalities arise early in the child's life and are improved with medical treatment. Since Kabuki syndrome was discovered relatively recently, very little is known regarding the average life span of individuals affected with the condition, however, present data on Kabuki syndrome does not point to a shortened life span.

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Mhanni, A.A., and A.E. Chudley. "Genetic Landmarks Through Philately—Kabuki Theater and Kabuki Syndrome." *Clinical Genetics* 56(August 1999): 116-117.

ORGANIZATIONS

CardioFacioCutaneous Support Network. 157 Alder Ave., McKee City, NJ 08232. (609) 646-5606.

Kabuki Syndrome Network. 168 Newshaw Lane, Hadfield, Glossop, SK13 2AY. UK 01457 860110. <http://www.ksn-support.org.uk>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

"Entry 147920: Kabuki Syndrome." *OMIM—Online Mendelian Inheritance in Man*. <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=147920>.

Oren Traub, MD, PhD

Kallmann syndrome

Definition

Kallmann syndrome is a disorder of hypogonadotropic hypogonadism, delayed puberty, and anosmia.

Description

Hypogonadotropic hypogonadism (HH) occurs when the body does not produce enough of two important hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH). This results in underdeveloped gonads and often infertility. Anosmia, the inability to smell, was first described with hypogonadotropic hypogonadism in 1856, but it was not until 1944 that Kallmann reported the **inheritance** of the two symptoms together in three separate families. Hence, the syndrome of hypogonadotropic hypogonadism and anosmia was named Kallmann syndrome (KS).

Kallmann syndrome (KS) is occasionally called dysplasia olfactogenitalis of DeMorsier. Affected people usually are detected in adolescence when they do not undergo puberty. The most common features are HH and anosmia, though a wide range of features can present in an affected person. Other features of KS may include a small penis or undescended testicles in males, kidney abnormalities, cleft lip and/or palate, **clubfoot**, hearing problems, and central nervous system problems such as synkinesia, eye movement abnormalities, and visual and hearing defects.

Genetic profile

Most cases of Kallmann syndrome are sporadic. However, some cases are inherited in an autosomal dominant pattern, an autosomal recessive pattern, or an X-linked recessive pattern. In most cells that make up a person there are structures called **chromosomes**. Chromosomes contain genes, which are instructions for how a person will grow and develop. There are 46 chromosomes, or 23 pairs of chromosomes, in each cell. The first 22 chromosomes are the same in men and women and are called the autosomes. The last pair, the sex chromosomes, are different in men and women. Men have an X and a Y chromosome (XY). Women have two X-chromosomes (XX). All the genes of the autosomes and the X-chromosomes in women come in pairs.

Autosomal dominant inheritance occurs when only one copy of a **gene** pair is altered or mutated to cause the condition. In autosomal dominant inheritance, the second normal gene copy cannot compensate, or make up for, the altered gene. People with autosomal dominant inheritance have a 50% chance of passing the gene and the condition onto each of their children.

KEY TERMS

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Hypothalamus—A part of the forebrain that controls heartbeat, body temperature, thirst, hunger, body temperature and pressure, blood sugar levels, and other functions.

Neuron—The fundamental nerve cell that conducts impulses across the cell membrane.

Pituitary gland—A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Puberty—Point in development when the gonads begin to function and secondary sexual characteristics begin to appear.

Synkinesia—Occurs when part of the body will move involuntarily when another part of the body moves.

Autosomal recessive inheritance occurs when both copies of a gene are altered or mutated to cause the condition. In autosomal recessive inheritance, the affected person has inherited one altered gene from their mother and the other altered gene from their father. Couples who both have one copy of an altered autosomal recessive gene have a 25% risk with each pregnancy to have an affected child.

X-linked recessive inheritance is thought to be the least common form of inheritance in KS, but is the most well understood at the genetic level. With X-linked recessive inheritance, the altered gene that causes the condition is on their X chromosome. Since men have only one copy of the X chromosome, they have only one copy of the genes on the X chromosome. If that one copy is altered, they will have the condition because they do not have a second copy of the gene to compensate. Women, however, can have one altered copy of the gene and not be affected as they have a second copy to compensate. In X-linked recessive conditions, women are generally not affected with the condition. Women who are carriers for an X-linked recessive condition have a 25% chance of having an affected son with each pregnancy.

Though all three patterns of inheritance have been suggested for Kallmann syndrome, as of 2001 only one gene has been found that causes Kallmann syndrome. The gene, KAL, is located on the X chromosome and is responsible for most cases of X-linked recessive Kallmann syndrome. The gene instructs the body to make a protein called anosmin-1. When this gene is altered in a male, Kallmann syndrome occurs. Of those families who have an X-linked recessive form of KS, approximately 1/2 to 1/3 have identifiable alterations in their KAL gene.

Demographics

Kallmann syndrome is the most frequent cause of hypogonadotropic hypogonadism and affects approximately 1/10,000 males and 1/50,000 females. Kallmann syndrome is found in all ethnic backgrounds. Because the incidence of KS in males is about five times greater than KS in females, the original belief was that the X-linked form of Kallmann syndrome was the most common. However, as of 2001, it is now assumed that the X-linked recessive form is the least common of all KS. The reason for Kallmann syndrome being more frequent in males is not known.

Signs and symptoms

Embryology

Normally, a structure in the brain called the hypothalamus makes a hormone called gonadotrophin releasing hormone (GnRH). This hormone acts on the pituitary gland, another structure in the brain, to produce the two hormones: follicle stimulating hormone (FSH) and luteinizing hormone (LH). Both of these hormones travel to the gonads where they stimulate the development of sperm in men and eggs in women. FSH is also involved in the release of a single egg from the ovary once a month. Hypogonadotropic hypogonadism results when there is an alteration in this pathway that results in inadequate production of LH or FSH. In Kallmann syndrome, the alteration is that the hypothalamus is unable to produce GnRH.

How hypogonadotropic hypogonadism and the inability to smell are related can be explained during the development of an embryo. The cells that eventually make the GnRH in the hypothalamus are first found in the nasal placode, part of the developing olfactory system (for sense of smell). The GnRH cells must migrate, or move, from the nasal placode up into the brain to the hypothalamus. These GnRH cells migrate by following the path of another type of cell called the olfactory neurons. Neurons are specialized cells that are found in the nervous system and have long tail-like structures called axons. The axons of the olfactory neurons grow from the nasal placode up into the developing front of the brain. Once they reach their final destination in the brain, they form the olfactory bulb, the structure in the brain that helps process odors allowing the sense of smell. The GnRH cells follow the pathway of the olfactory neurons up into the brain to reach the hypothalamus.

In Kallmann syndrome, the olfactory neurons are unable to grow into the brain. Hence, the GnRH cells can not follow their pathway. As a result, the olfactory bulb does not form, resulting in the inability to smell. The GnRH cells can not follow the pathway of the axons and do not reach their final destination in the hypothalamus. Hence, no GnRH is made to stimulate the pituitary to make FSH and LH, resulting in hypogonadotropic hypogonadism.

In X-linked recessive KS, the KAL gene instructs the body to make the protein anosmin-1. This protein is involved in providing the pathway in the brain for which the olfactory axons grow. If it is altered in any way, the axons will not know where to grow in the brain and the GnRH cells will be unable to follow. The protein anosmin-1 is also found in other parts of the body, possibly explaining some of the other symptoms sometimes seen in Kallmann syndrome.

Other features

The features of Kallmann syndrome can vary among affected individuals even within the same family. The two features most often associated with Kallmann syndrome are HH and the inability to smell. Males can also have a small penis and undescended testicles at birth (testicles are still in body and have not dropped down into the scrotal sac). Clubfoot, cleft lip and/or cleft palate can also be present at birth. Clubfoot occurs when one or both feet are not properly placed onto the legs and can appear turned. Cleft lip and/or cleft palate occur when the upper lip and/or the roof of the mouth fail to come together during development. Kidney abnormalities, most often unilateral renal agenesis (one kidney did not form) are especially common in those males with X-linked recessive KS. Choanal atresia (pathway from the nose is blocked at birth) and structural heart defects have also been seen in KS.

Central nervous system problems can also occur in Kallmann syndrome. These can include nystagmus (involuntary eye movement), ataxia (involuntary body movement), hearing loss and problems with vision. Synkinesia is especially common in men with the X-linked recessive form of KS. Some people with KS are also mentally retarded. **Holoprosencephaly**, when the brain fails to develop in two halves, can also be seen in some individuals with KS.

Diagnosis

Individuals with Kallmann syndrome are usually diagnosed when they do not undergo puberty. Hormone testing shows that both LH and FSH are decreased. Affected individuals often do not realize they cannot smell. MRI can often detect the absence of the olfactory bulb in the brain. Renal ultrasound can determine if a kidney is missing.

As of 2001, **genetic testing** for alterations in the KAL gene is the only genetic testing available. Even with families with clear X-linked recessive inheritance, genetic testing does not always detect an alteration in the KAL gene. Hence, diagnosis is still very dependent upon clinical features.

Treatment and management

When a child with KS is born with structural abnormalities such as cleft lip and/or palate, clubfoot or heart defects, surgery is often required to fix the defect. Taking sex hormones treats delayed puberty; women take estrogen and men take testosterone. Once puberty is completed, taking GnRH or both LH and FSH can treat hypogonadism. For most affected individuals, treatment is successful and infertility is reversed. However, a small portion of people will not respond to treatment.

When an isolated case of Kallmann syndrome is diagnosed, evaluation of first-degree family members, such as parents and siblings, should be completed. This should include a detailed family history, measuring hormone levels, assessing sense of smell, and renal ultrasound to look for kidney abnormalities. This information may help to diagnosis previously unrecognized cases of Kallmann syndrome. Furthermore, this information may be important for **genetic counseling** and determining whom in the family is at risk for also having Kallmann syndrome.

Prognosis

For individuals with the most common features of Kallmann syndrome, hypogonadism and the inability to smell, prognosis is excellent. In most cases, hormone treatment is able to reverse the delayed puberty and hypogonadism. For those individuals with other symptoms of Kallmann syndrome, prognosis can depend on how severe the defect is. For example, structural heart defects can be quite complex and sometimes surgery can not fix them. Furthermore, no treatment is available for the mental retardation in the portion of affected individuals with this symptom.

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American Society for Reproductive Medicine. 1209 Montgomery Highway, Birmingham, AL 35216-2809. (205) 978-5000. <http://www.asrm.com>.

RESOLVE, The National Infertility Association. 1310 Broadway, Somerville, MA 02144-1779. (617) 623-0744. resolveinc@aol.com. <http://www.resolve.org>.

WEBSITES

Pediatric Database (PEDBASE) <www.icondata.com/health/pedbase/files/KALLMANN.HTM>.

Carin Lea Beltz, MS

Kartagener syndrome

Definition

Kartagener (pronounced KART-agayner) syndrome refers to a condition that involves difficulty with clearing mucus secretions from the respiratory tract, male infertility, and situs inversus. The defining characteristic of this syndrome is the situs inversus, which is a reversal of abdominal and thoracic organs.

Description

This syndrome is named after Kartagener, a physician from Switzerland. In the 1930's, Kartagener and a colleague described a familial form of bronchiectasis with situs inversus and nasal polyps. This came to be known as Kartagener syndrome. Kartagener syndrome is also known as the Siewert syndrome, after another physician, Siewert, who described the syndrome in the early 1900's.

Individuals who have Kartagener syndrome form a subset of the disorder called primary ciliary dyskinesia. Originally, primary ciliary dyskinesia was known as immotile cilia syndrome. The name, immotile cilia syndrome, is no longer used since the discovery that the cilia are actually not immotile, but rather, abnormal in movement. Individuals who have Kartagener syndrome, basically have primary ciliary dyskinesia, plus partial or complete situs inversus. The situs inversus is what sets Kartagener syndrome apart from primary ciliary dyskinesia.

Kartagener syndrome is caused by abnormalities of the cilia that line the respiratory tract and also form the flagella of sperm. Cilia are tiny hair-like structures that contain a bundle of small parallel tubes that form a central core. This core is called the axoneme. Ciliary movement is accomplished by the bending of the axoneme. One of the most important associated structures that enable ciliary movement to occur are sets of tiny arms that project from each tubule. These tiny arms are called dynein arms.

Cilia line the cells of the lungs, nose and sinuses. Before reaching the lungs, air travels through the airway where it is moistened and filtered. The nasal passages and airway are lined with mucus membranes. The mucus covering the mucus membrane traps dirt and other foreign particles that have been breathed in. The cilia, lining the membranes, beat in a wavelike manner moving the layer of mucus and carrying away the dirt and debris that has been trapped. This mucus can then be coughed out or swallowed into the stomach.

In Kartagener syndrome, the cilia do not move, move very little, or move abnormally. Because the cilia do not function properly, the mucus is not cleared from the respiratory tract, which leads to sinus infection (sinusitis) and chronic changes of the lung (bronchiectasis), which make it difficult to exhale. Mucus clearance from the middle ear can also be affected and over time can lead to hearing loss.

The male infertility in Kartagener syndrome is also caused by abnormal cilia movement. One spermatozoon consists of a head, midpiece, and a tail or flagellum. The tail of a spermatozoon is a long flagellum consisting of a central axoneme. This axoneme enables the movement of the flagellum so that the spermatozoon can propel its way to the fallopian tube and burrow through the egg coat to fertilize the egg. In Kartagener syndrome, these cilia are either immotile, or are not able to move normally to complete the journey to the fallopian tubes, nor may they be able to burrow through the egg coat. This results in male infertility.

As stated above, situs inversus is what sets Kartagener syndrome apart from primary ciliary dyskinesia. Complete situs inversus involves reversal of both the abdominal and thoracic organs so that they form a mirror image of normal. In partial situs inversus, the thoracic organs may be reversed, while the abdominal organs are normally positioned, or vice versa. Approximately one in 10,000 adults have situs inversus. Only about 20% of individuals who have complete situs inversus are diagnosed to have Kartagener syndrome. Of those with complete situs inversus who are diagnosed to have Kartagener syndrome, there is only a small risk for associated cardiac defects. Partial situs inversus may occur in individuals who have Kartagener syndrome as well. Partial situs inversus has a higher association with other abnormalities, including polysplenia or **asplenia** (extra or absent spleen) and cardiac defects.

One theory behind the association of situs inversus with the underlying cause of Kartagener syndrome is that the lack of ciliary movement in the developing embryo

may result in incorrect organ rotation in approximately 50% of affected individuals. In fact, 50% of patients with PCD will have situs inversus and thus be diagnosed to have Kartagener syndrome. However, this is a theory supported only by some researchers.

Genetic profile

Kartagener syndrome is an autosomal recessive condition. This means that in order to have the condition, an individual needs to inherit two copies of the **gene** for the condition, one from each parent. Individuals who carry only one gene for an autosomal recessive syndrome are called heterozygotes. Heterozygotes for Kartagener syndrome have normal ciliary function and do not have any clinical features of the condition. If two carriers of Kartagener syndrome have children, there is a 25% chance, with each pregnancy, for having a child with Kartagener syndrome.

The components that form the cilium contain several hundred different proteins. Each is coded for by different **DNA** sequences, potentially on different **chromosomes**. A defect in any of these codes could produce an abnormal or missing protein that is a building block for the cilium and thus could cause abnormal ciliary structure and movement, resulting in Kartagener syndrome.

When the same condition can be caused by different genetic abnormalities, this is known as genetic heterogeneity. In fact, several different defects in cilia have been seen in association with Kartagener syndrome, including; overly long cilia, overly short cilia, absent cilia and randomly oriented cilia, suggesting genetic heterogeneity. Studies have suggested that the most common defect of cilia in Kartagener syndrome is the lack of dynein arms. There have been rare cases in which individuals have Kartagener syndrome, yet have no detectable abnormality of the cilia, even though the ciliary function is abnormal. Results of one study involving a genome-wide linkage search performed on 31 families, with multiple individuals affected with either PCD or Kartagener syndrome, strongly suggested extensive heterogeneity. Potential regions involving genes responsible for PCD or Kartagener syndrome were localized on chromosomes 3, 4, 5, 7, 8, 10, 11, 13, 15, 16, 17 and 19.

Demographics

Kartagener syndrome occurs in approximately one in 32,000 live births, which is half the incidence of primary ciliary dyskinesia (one in 16,000 live births). Kartagener syndrome is not found more commonly in any particular sex, ethnic background or geographic region. Males, however, may be diagnosed more often than females because of infertility investigation.

KEY TERMS

Bronchiectasis—An abnormal condition of the bronchial tree, characterized by irreversible widening and destruction of the bronchial walls of the lungs.

Cystic fibrosis—A respiratory disease characterized by chronic lung disease, pancreatic insufficiency and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encodes a transmembrane receptor.

Dyskinesia—Impaired ability to make voluntary movements.

Tympanoplasty—Any of several operations on the eardrum or small bones of the middle ear, to restore or improve hearing in patients with conductive hearing loss.

Signs and symptoms

Newborns who have Kartagener syndrome may present with neonatal respiratory distress. Often when individuals are diagnosed to have Kartagener syndrome in later childhood, problems such as neonatal respiratory distress may be identified in their history. Symptoms that may present in childhood include; recurrent ear infections (otitis media) that can lead to hearing loss, chronic productive cough, reactive airway disease, pneumonia, chronic bronchitis, runny nose (rhinitis) with a thin discharge, and sinus infection (sinusitis). Situs inversus usually does not present symptomatically, unless it is associated with a congenital heart defect.

The most common clinical expression of Kartagener syndrome in adults includes chronic upper and lower airway disease presenting as sinusitis and bronchiectasis. Clubbing of the digits (fingers) may occur as the result of chronic hypoxia (lack of oxygen) from bronchiectasis. In males of reproductive age, male infertility is almost universal. In females who have Kartagener syndrome, infertility is not usually a characteristic. This suggests that the egg transport down the fallopian tube is associated more with muscle contractions than with ciliary movement.

Several other conditions should be considered when the aforementioned symptoms present, including; **Cystic fibrosis** (CF), immune deficiencies and severe allergies. Although the causes of Kartagener syndrome and CF are completely different, the symptoms of these two diseases

are very similar. Often when the symptoms present, children with Kartagener syndrome are tested for CF first because the incidence of CF is much higher (one in 2,400) than the incidence of Kartagener syndrome. CF is also associated with male infertility.

Diagnosis

Diagnosis of Kartagener syndrome is confirmed by identifying the ciliary abnormalities of structure and movement. This is accomplished by biopsy of the mucus membranes of the respiratory tract and/or by examination of sperm, looking for ciliary dyskinesia. Situs inversus can be identified by x ray or ultrasound examination. Infertility investigation may elicit the possibility of Kartagener syndrome in a patient previously undiagnosed. After a diagnosis is made, **genetic counseling** should be provided to discuss the **inheritance** pattern, to help identify other possible affected family members and to discuss reproductive options.

As Kartagener syndrome is an autosomal recessive disorder, individuals who have had a child with Kartagener syndrome have a 25% chance, with each future pregnancy, of having another child with Kartagener syndrome. Prenatal diagnosis may be possible for a couple with a previously affected child, by performing ultrasound examination to identify a fetus who has situs inversus. Although, if the fetus does not exhibit situs inversus, it is still possible for the fetus to have PCD. Also, it is important to remember that identifying a fetus who has situs inversus in a family not known to be at an increased risk for Kartagener syndrome, does not mean that the fetus has Kartagener syndrome as only 20% of individuals who have situs inversus have Kartagener syndrome. As of January 2001, DNA testing for Kartagener syndrome is not possible.

Treatment and management

Treatment for Kartagener syndrome involves treatment of the symptoms. Treatment for sinusitis includes the use of antibiotics to treat and prevent recurrent infection. Occasionally, surgery to relieve the sinusitis and remove nasal polyps that may be present is necessary. Daily chest physiotherapy to loosen mucus secretions is a common therapy as well, and if started early in life can help to prevent or delay development of bronchiectasis. Tympanoplasty in children with recurrent ear infections is often necessary.

Advances in reproductive technology allow for men who have Kartagener syndrome to have the opportunity to have children. A procedure called intracytoplasmic sperm injection or ICSI, now allow immotile or dysmotile sperm to fertilize an egg. ICSI involves injection of a single sperm into single eggs in order for fertilization to occur. This procedure first involves ovulation induction and egg retrieval to obtain eggs for attempt at fertilization by ICSI. In Vitro Fertilization (ICSI) pregnancy rates vary from center to center. Overall pregnancy rates of 10%-40% have been quoted worldwide, utilizing these procedures.

The chance for an affected male and his unaffected partner to have a child who has Kartagener syndrome is small. If the disease incidence is one in 32,000, then the chance for the unaffected woman to be a carrier of Kartagener syndrome is approximately one in 100 and the chance for having an affected child would be expected to be approximately one in 200 (0.5%). However, all children of affected males or females will be carriers for Kartagener syndrome.

Prognosis

The severity of Kartagener syndrome is variable. With the advent of antibiotic use for infection control, the life expectancy of a patient with Kartagener syndrome is close to or within the normal range, if there are no immediate problems in the newborn period.

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ORGANIZATIONS

American Lung Association. 1740 Broadway, New York, NY 10019-4374. (212) 315-8700 or (800) 586-4872. <http;//www.lungusa.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Renee A. Laux, MS

Karyotype

Definition

Karyotype refers to the arrangement of **chromosomes** in their matched (homologous) pairs. For the purposes of this definition, we will be referring to human chromosomes, although there is a karyotype characteristic for each species. The human chromosomes are arranged and numbered according to the International System for Human Cytogenetic Nomenclature (ISCN). The most recent recommendations of the ISCN are from 1995. Karyotype either refers to the actual composition of the chromosomes in a body cell of an individual or species, or to the actual diagram or photograph of those chromosomes, arranged in their pairs.

Description

The normal human karyotype consists of 23 pairs of chromosomes. There are 22 pair of autosomes, which are the chromosomes that are not the sex chromosomes. The genes on these chromosomes instruct our bodies as to how they look and function. The 23rd pair of chromosomes are the sex chromosomes. Typically, females have two X sex chromosomes and males have one X sex chromosome and one Y sex chromosome.

Karyotype construction

In the construction of the karyotype, the chromosomes are numbered 1 to 22 from longest to shortest. The last pair are the sex chromosomes and are placed on the karyotype after the 22nd pair. The chromosomes can be separated into groups, based on their length and the position of the centromere. Group A consists of chromosome pairs 1, 2 and 3. They are the longest chromosomes and their centromeres are in the center of the chromosomes (metacentric). Group B consists of chromosome pairs 4 and 5. They are long; however, their centromeres lie toward the top of the chromosomes (submetacentric). Group C consists of chromosome pairs 6, 7, 8, 9, 10, 11 and 12 and also includes the X chromosome. They are medium-sized and their centromeres either lie in the middle or toward the top of the chromosomes. Group D consists of chromosome pairs 13,14 and 15. They are medium-sized and their centromeres lie at the top of the chromosomes (acrocentric). Additionally, the D group chromosomes have satellites. Group E consists of chromosome pairs 16, 17 and 18. They are relatively short chromosomes and their centromeres lie in the center or towards the top of the chromosomes. Group F consists of chromosomes 19 and 20. They are short chromosomes with centromeres that lie in the center of the chromosome. Lastly, group G consists of chromosome pairs 21, 22 and the Y chromosome. These are short chromosomes with their centromeres at the top. Chromosome pairs 21 and 22 have satellites. The Y chromosome does not have satellites.

KEY TERMS

Acrocentric—A chromosome with the centromere positioned at the top end.

Centromere—The centromere is the constricted region of a chromosome. It performs certain functions during cell division.

Homologous chromosomes—Homologous chromosomes are two chromosomes of a doublet set that are identical, particularly for the genes that are on them.

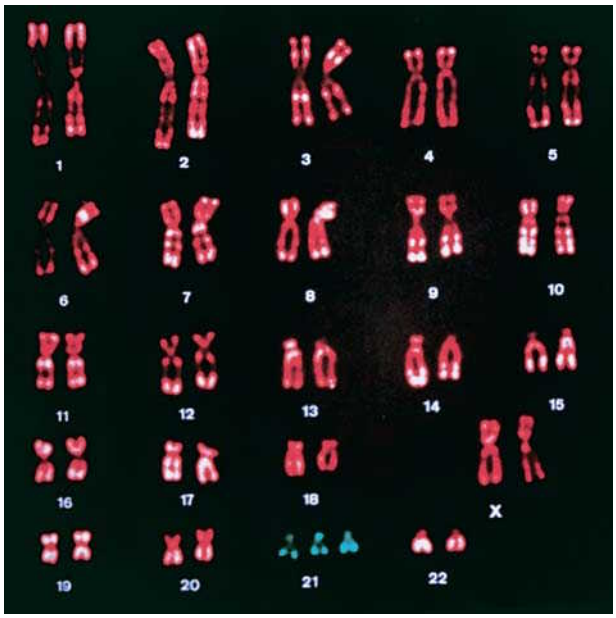
Metacentric—When a chromosome has the centromere in the middle of the chromosome it is called a metacentric chromosome.

Satellites of chromosomes—Small segments of genetic material at the tips of the short arms of chromosomes 13, 14, 15, 21, and 22.

Submetacentric—Positioning of the centromere between the center and the top of the chromosome.

The actual chromosomes are only individually distinguishable during a certain stage of cell division. This stage is called the metaphase stage. Chromosome preparations are made from pictures of the chromosomes during the metaphase stage of division. The metaphase spread is what the technician sees in one cell under the microscope and what the photograph of that one cell is referred to. Usually, the chromosomes in a metaphase preparation are banded by special staining techniques used in the laboratory. Each numbered chromosome is unique in its banding pattern so that all number 1s look the same and all number 2s look the same, etc. Although, there can be small normal familial variations in chromosomes. Because of banding, the chromosomes are more easily distinguishable from each other and the banding makes it is easier to see differences or abnormalities. For example, if a chromosome is missing a piece, or two chromosomes are attached to each other (translocation), it is much easier to see with banded chromosomes than with unbanded chromosomes.

Chromosome preparations can be made from any potentially dividing cells, including; blood cells, skin cells, amniotic fluid cells (the fluid surrounding an



Karyotype showing three copies of chromosome 21. This indicates Down syndrome. *(Custom Medical Stock Photo, Inc.)*

unborn baby), placental tissue or chorionic villi (tissue that forms the placenta and can be used in prenatal diagnosis).

ISCN formulas exist to describe any chromosome complement. The basic formula for writing a karyotype is as follows. The first item written is the total number of chromosomes, followed by a comma. The the second item written is the sex chromosome complement. The typical female karyotype is written as 46,XX and the typical male karyotype is written as 46,XY.

Formulas for abnormal karyotypes

Many formulas for writing abnormal karyotypes have been determined. Some common examples follow. A plus or a minus sign before a chromosome number is used to show that the entire chromosome is extra or missing. Also, the total number of chromosomes will be different than 46. For example, the condition **Down syndrome** occurs when an individual has an extra number 21 chromosome. For a male, this karyotype is written as 47,XY,+21. An individual may also have extra or missing parts of chromosomes. The short arm of a chromosome is called the p arm and the long arm is called the q arm. For example, the condition **Wolf-Hirschhorn syndrome** is caused by a missing part of the top arm of chromosome 4. For a female, this karyotype would be written as 46,XX,del(4)(p16). The chromosome that is involved in the change is specified within the first set of parentheses and the breakpoint for the missing material is defined in the second set of parentheses. A final example is a balanced translocation karyotype. A balanced translocation means that there is no missing or extra genetic material as the result of the translocation. There are many types of translocations. One type is called a robertsonian translocation. A robertsonian translocation occurs when two acrocentric chromosomes are attached together. One common example is a translocation involving chromosomes 13 and 14. If a male has a balanced robertsonian translocation of chromosomes 13 and 14, this is written as 45,XY,der(13;14). The “der” stands for derivative, as the new 13;14 chromosome is considered a derivative. There are only 45 separate chromosomes now, which is why 45 is the number written in the karyotype. There are many more formulas for the abundant abnormal chromosome findings in individuals. For further detailed information, please refer to the resource listed below.

Resources

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Renee A. Laux, MS

Karyotype analysis *see* **Karyotype**

Keller syndrome *see* **FG syndrome**

Kennedy disease

Definition

Kennedy disease (KD) is a disorder characterized by degradation of the anterior horn cells of the spinal cord resulting in slow progressive muscle weakness and atrophy. Men with Kennedy disease often have breast enlargement (gynecomastia), testicular atrophy, and may have infertility.

Description

Kennedy disease, also referred to as spinobulbar muscular atrophy (SBMA), arises primarily from degradation of the anterior horn cells of the spinal cord, resulting in proximal weakness and atrophy of voluntary skeletal muscle. Anterior horn cells control the voluntary muscle contractions from large muscle groups such as the arms and legs. For example, if an individual wants to move his/her arm, electrical impulses are sent from the brain to the anterior horn cells to the muscles of the arm, which then stimulate the arm muscles to contract, allow-

ing the arm to move. Degradation is a rapid loss of functional motor neurons. Loss of motor neurons results in progressive symmetrical atrophy of the voluntary muscles. Progressive symmetrical atrophy refers to the loss of function of muscle groups from both sides of the body. For example, both arms and both legs are equally affected by similar degrees of muscle loss and the inability to be controlled and used properly. Progressive loss indicates that muscle loss is not instantaneous, rather muscle loss occurs consistently over a period of time. These muscle groups include those skeletal muscles that control large muscle groups such as the arms, legs and torso. The weakness in the legs is generally greater than the weakness in the arms.

Proximal weakness is in contrast to distal weakness, and indicates that muscles such as the arms and the legs are affected rather than the muscles of the hands, feet, fingers, and toes. However, the motor neuron of the brainstem and sensory neurons of the dorsal root ganglia are also affected in KD. Motor neurons are the neurons that control large muscle groups (arms, legs, torso) of which anterior horn cells are a subgroup. Sensory neurons are a distinct class of neurons that control an individual's senses. An example would be pain receptors that cause an involuntary reaction to a stimuli such as when a person accidentally grasps a boiling hot kettle and immediately releases the kettle. Dorsal root ganglia are analogous to a headquarters for neurons, through which essentially all neuronal stimuli are processed.

KEY TERMS

Anterior horn cells—Subset of motor neurons within the spinal cord.

Atrophy—Wasting away of normal tissue or an organ due to degeneration of the cells.

Degradation—Loss or diminishing.

Dorsal root ganglia—The subset of neuronal cells controlling impulses in and out of the brain.

Intragenic—Occuring within a single gene.

Motor neurons—Class of neurons that specifically control and stimulate voluntary muscles.

Motor units—Functional connection with a single motor neuron and muscle.

Sensory neurons—Class of neurons that specifically regulate and control external stimuli (senses: sight, sound).

Transcription—The process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

Voluntary muscle—A muscle under conscious control, such as arm and leg muscles.

Diagnosis

Kennedy disease is suspected clinically in a male with an early adulthood onset of proximal muscle weakness of the limbs, fasticulations (small local contractions of the musculature that is visible through the skin) of the tongue, lips or area around the mouth, absence of hyperactive reflexes and spasticity, and often evidence of enlarged breasts and/or small testes with few or no sperm.

The diagnosis is made by a specific molecular genetic test that measures the number of "repeats" in a particular part of the androgen receptor (AR) **gene**. The alteration of the AR gene that causes Kennedy disease is an expansion of a CAG trinucleotide repeat in the first PART of the gene. In unaffected individuals, between 11 to 33 copies OF the CAG trinucleotide are present. In patients with Kennedy disease, this number rises to 40 to 62. The greater the number of expanded repeats, the earlier the age of onset.

Genetic profile

Kennedy disease is an X-linked recessive disease, meaning the abnormal gene is found on the X chromosome and two copies of the abnormal gene must be present for the disorder to occur. Since males only inherit one X chromosome (the other is the Y chromosome) they will always express an X-linked disorder if the abnormal gene is on the X chromosome they receive. Females on the other hand inherit two X **chromosomes**. Even if one X chromosome contains the abnormal gene, the second X chromosome with a normal functioning gene can usually compensate for the other. Males lack the second X chromosome that may be able to mask the effect of the abnormal gene.

The disease was first characterized in 1968. The KD-determining gene, androgen receptor (AR), maps to the proximal long arm of the X-chromosome.

The AR protein is a member of the steroid-thyroid hormone receptor family and is involved in transcription regulation. Transcription regulation is the molecular process that controls the "reading" of the genetic **DNA** information and turning it into **RNA** which is the material which generates proteins.

Demographics

Because of the X-linked **inheritance** pattern of Kennedy disease, only males are affected by this disor-

der. Females may be carriers of the disease if they possess an abnormal gene on one of her X chromosomes. Due to the rare nature of this disease, and the fact that it may frequently be misdiagnosed as another form of neuromuscular disease, no particular race or ethnicity appears to be at greater risk than another.

Kennedy disease is primarily an adult disease, with an onset between the third and fifth decade of life. Once symptoms present, the disease is slowly progressive. In addition to neuronal cell loss, breast enlargement (gynecomatia), reduced fertility and testicular atrophy have also been reported in affected males.

Treatment and management

To date, there is not treatment for SBMA. However, there are possible mechanisms through which treatment could be developed. **Gene therapy** could be used for SBMA to replace the abnormal gene associated with SBMA with a copy carrying fewer CAG repeats. Currently this is not possible or available.

As the bulbar muscles of the face are affected, eating and swallowing can become difficult. Due to the weakening of the respiratory muscles, breathing can also be labored. It is therefore essential for patients to undergo chest physiotherapy (CPT). CPT is a standard set of procedures designed to trigger and aid coughing in patients. Coughing is important as it clears the patient's lungs and throat of moisture and prevents secondary problems, such as pneumonia.

As symptoms progress, patients may require a ventilator to aid breathing.

Prognosis

The majority of patients with SBMA have a normal life span. About 10% of older, severely affected patients with SBMA may die from pneumonia or asphyxiation secondary to weakness of the bulbar muscles.

Resources

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ORGANIZATIONS

Kennedy Disease (SBMA) Support Group. 1804 Quivira Road, Washington, KS 66968. (785) 325-2629. gryphon @grapevine.net. <http://www.geocities.com/HotSprings/Villa/1989>.

National Ataxia Foundation. 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447. (763) 553-0020. Fax: (763) 553-0167. naf@mr.net. <http://www.ataxia.org/>.

WEBSITES

Families of Spinal Muscular Atrophy. <http://www.fsma.org>.

The Andrew's Buddies web site. *FightSMA.com* <http://www.andrewsbuddies.com/news.html>.

Muscular Dystrophy Association. <http://www.mdausa.org>.

Philip J. Young
Christian L. Lorson, PhD

Ketotoic hyperglycinemia *see* **Propionic acidemia**

Kinky hair disease *see* **Menkes syndrome**

Klein-Waardenburg syndrome, *see* **Waardenburg syndrome**

Klinefelter syndrome

Definition

Klinefelter syndrome is a chromosome disorder in males. People with this condition are born with at least one extra X chromosome.

Description

Klinefelter syndrome is a condition where one or more extra X-chromosomes are present in a male. Boys with this condition appear normal at birth. They enter puberty normally, but by mid-puberty have low levels of testosterone causing small testicles and the inability to make sperm. Affected males may also have learning disabilities and behavior problems such as shyness and immaturity and are at an increased risk for certain health problems.

Genetic profile

Chromosomes are found in the cells in the body. Chromosomes contain genes, structures that tell the body how to grow and develop. Chromosomes are responsible for passing on hereditary traits from parents to child. Chromosomes also determine whether the child will be

male or female. Normally, a person has a total of 46 chromosomes in each cell, two of which are responsible for determining that individual's sex. These two sex chromosomes are called X and Y. The combination of these two types of chromosomes determines the sex of a child. Females have two X chromosomes (the XX combination); males have one X and one Y chromosome (the XY combination).

In Klinefelter syndrome, a problem very early in development results in an abnormal number of chromosomes. Most commonly, a male with Klinefelter syndrome will be born with 47 chromosomes in each cell, rather than the normal number of 46. The extra chromosome is an X chromosome. This means that rather than having the normal XY combination, the male has an XXY combination. Because people with Klinefelter syndrome have a Y chromosome, they are all male.

Approximately one-third of all males with Klinefelter syndrome have other chromosome changes involving an extra X chromosome. Mosaic Klinefelter syndrome occurs when some of the cells in the body have an extra X chromosome and the other have normal male chromosomes. These males can have the same or milder symptoms than non-mosaic Klinefelter syndrome. Males with more than one additional extra X chromosome, such as 48,XXXY, are usually more severely affected than males with 47,XXY.

Klinefelter syndrome is not considered an inherited condition. The risk of Klinefelter syndrome reoccurring in another pregnancy is not increased above the general population risk.

Demographics

Klinefelter syndrome is one of the most common **chromosomal abnormalities**. About one in every 500 to 800 males is born with this disorder. Approximately 3% of the infertile male population have Klinefelter syndrome.

Signs and symptoms

The symptoms of Klinefelter syndrome are variable and not every affected person will have all of the features of the condition. Males with Klinefelter syndrome appear normal at birth and have normal male genitalia. From childhood, males with Klinefelter syndrome are taller than average with long limbs. Approximately 20–50% have a mild intention tremor, an uncontrolled shaking. Many males with Klinefelter syndrome have poor upper body strength and can be clumsy. Klinefelter syndrome does not cause homosexuality. Approximately one-third of males with Klinefelter syndrome have breast growth, some requiring breast reduction surgery.

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Gonadotrophin—Hormones that stimulate the ovary and testicles.

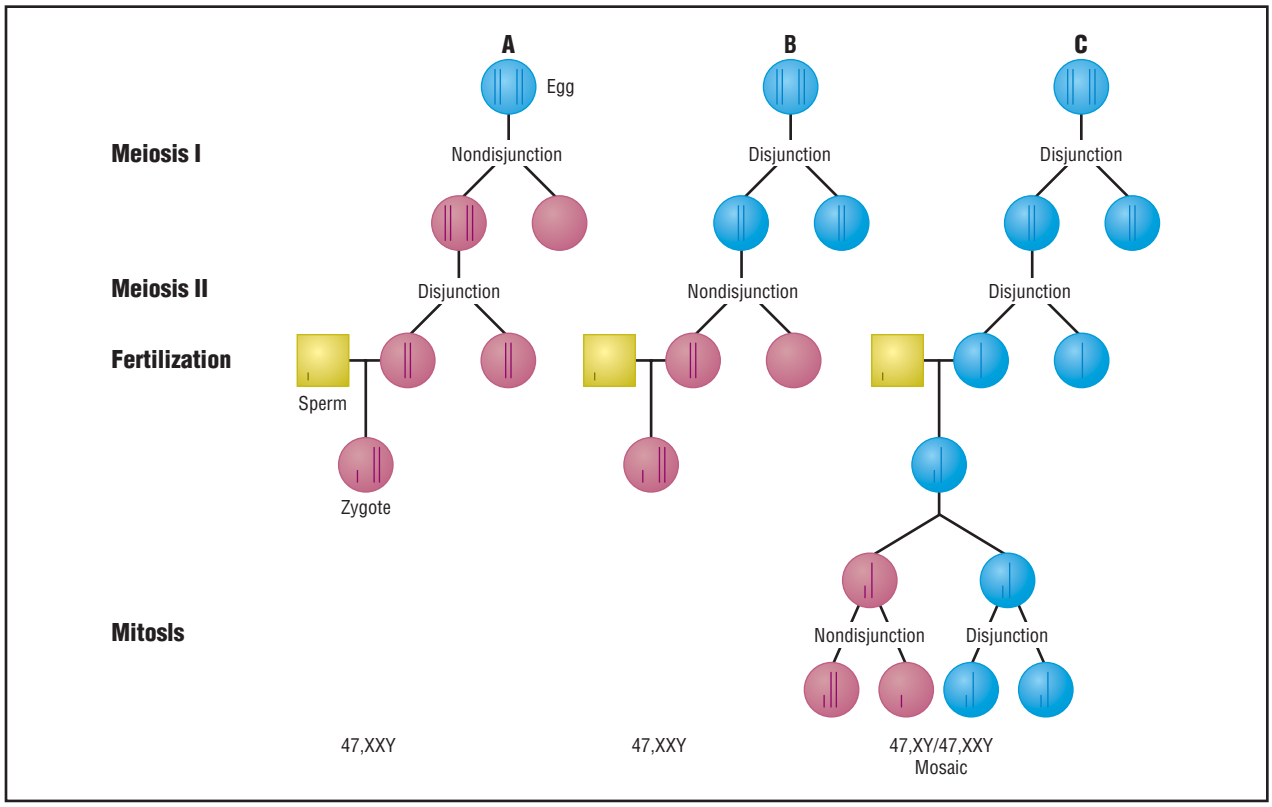
Testosterone—Hormone produced in the testicles that is involved in male secondary sex characteristics.

Most boys enter puberty normally, though some can be delayed. The Leydig cells in the testicles usually produce testosterone. With Klinefelter syndrome, the Leydig cells fail to work properly causing the testosterone production to slow. By mid-puberty, testosterone production is decreased to approximately half of normal. This can lead to decreased facial and pubic hair growth. The decreased testosterone also causes an increase in two other hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH). Normally, FSH and LH help the immature sperm cells grow and develop. In Klinefelter syndrome, there are few or no sperm cells. The increased amount of FSH and LH cause hyalinization and fibrosis, the growth of excess fibrous tissue, in the seminiferous tubules where the sperm are normally located. As a result, the testicles appear smaller and firmer than normal. With rare exception, men with Klinefelter syndrome are infertile because they can not make sperm.

While it was once believed that all boys with Klinefelter syndrome were mentally retarded, doctors now know that the disorder can exist without retardation. However, children with Klinefelter syndrome frequently have difficulty with language, including learning to speak, read, and write. Approximately 50% of males with Klinefelter syndrome are dyslexic.

Some people with Klinefelter syndrome have difficulty with social skills and tend to be more shy, anxious, or immature than their peers. They can also have poor judgement and do not handle stressful situations well. As a result, they often do not feel comfortable in large social gatherings. Some people with Klinefelter syndrome can also have anxiety, nervousness, and/or **depression**.

The greater the number of X-chromosomes present, the greater the disability. Boys with several extra X-chromosomes have distinctive facial features, more severe



Nondisjunction, failure of paired chromosomes to separate, can result at different stages of meiosis or mitosis. When nondisjunction occurs in the first (A) or second (B) phase of meiosis the resulting karyotype will be 47,XXY. If the chromosomes fail to separate during mitosis (C) a mosaic kayrotype (46,XY/47,XXY) will result. *(Gale Group)*

retardation, deformities of bony structures, and even more disordered development of male features.

Diagnosis

Diagnosis of Klinefelter syndrome is made by examining chromosomes for evidence of more than one X chromosome present in a male. This can be done in pregnancy with prenatal testing such as a chorionic villus sampling or **amniocentesis**. Chorionic villus sampling is a procedure done early in pregnancy (approximately 10–12 weeks) to obtain a small sample of the placenta for testing. An amniocentesis is done further along in pregnancy (from approximately 16–18 weeks) to obtain a sample of fluid surrounding the baby for testing. Both procedures have a risk of miscarriage. Usually these procedures are done for a reason other than diagnosing Klinefelter syndrome. For example, a prenatal diagnostic procedure may be done on an older woman to determine if her baby has **Down syndrome**. If the diagnosis of Klinefelter syndrome is suspected in a young boy or adult male, chromosome testing can also be on a small blood or skin sample after birth.

Treatment and management

There is no treatment available to change chromosomal makeup. Children with Klinefelter syndrome may benefit from a speech therapist for speech problems or other educational intervention for learning disabilities. Testosterone injections started around the time of puberty may help to produce more normal development including more muscle mass, hair growth, and increased sex drive. Testosterone supplementation will not increase testicular size, decrease breast growth, or correct infertility.

Prognosis

While many men with Klinefelter syndrome go on to live normal lives, nearly 100% of these men will be sterile (unable to produce a child). However, a few men with Klinefelter syndrome have been reported who have fathered a child through the use of assisted fertility services. Males with Klinefelter syndrome have an increased risk of several conditions such as **osteoporosis**, autoimmune disorders such as lupus and arthritis, diabetes, and both breast and germ cell tumors.

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American Association for Klinefelter Syndrome Information and Support (AAKSIS) 2945 W. Farwell Ave., Chicago, IL 60645-2925. (773) 761-5298 or (888) 466-5747. Fax: (773) 761-5298. <http://www.aaksis.org aaksis@aaksis.org>.

Klinefelter Syndrome and Associates, Inc. PO Box 119, Roseville, CA 95678-0119. (916) 773-2999 or (888) 999-9428. Fax: (916) 773-1449. ksinfo@genetic.org. <http://www.genetic.org/ks>.

Klinefelter's Organization. PO Box 60, Orpington, BR68ZQ. UK <http://hometown.aol.com/KSCUK/index.htm>.

WEBSITES

Klinefelter Syndrome Support Group Home Page. <http://klinefeltersyndrome.org/index.html>.

Carin Lea Beltz, M.S.

Klippel-Feil sequence

Definition

Individuals with Klippel-Feil sequence (KFS) were originally described as having a classic triad of webbed neck (very short neck), low hairline, and decreased flexibility of the neck. More commonly, abnormal joining or fusion of two or more vertebrae (bones) of the cervical spine (neck bones) characterizes Klippel-Feil sequence.

Description

Klippel-Feil sequence is extensive fusion of multiple cervical vertebrae (the uppermost bones of the spine). There may be complete fusion or multiple irregular bony segments in the bones of the upper back (cervical and often upper thoracic spine). Premature and extensive arthritis and osseous (bony) spurring affecting the joints of the spine (facet joints) are common in individuals with Klippel-Feil sequence.

There are three classifications of Klippel-Feil sequence.

- Group 1 exhibits fusion of the lower skull (head) and the first bone of the spine (the first cervical vertebrae (C1)). The second and third spinal bones (cervical vertebrae C2 and C3) are also usually fused together in Group 1. The normal cervical spine has seven bones or vertebrae. Normally half of the ability of humans to bend their heads forward (flexion) and backwards (extension) occurs in the joints between the base of the skull and the uppermost spinal bone. The other half of the motions of flexion and extension occur in the rest of the upper spine. Therefore, the danger is due to the excessive motion of the neck between the joints that are fused.
- Group 2 has fusion of bones (vertebrae) below the second cervical bone (C2). Group 2 also has an abnormal skull and upper spinal bone connection.
- Group 3 has an open space between two fused segments of spinal bones.

Genetic profile

Although this is usually a sporadic occurrence, an abnormal **gene** responsible for Klippel-Feil sequence has been found on the q (long) arm of chromosome 8. The human cell contains 46 **chromosomes** arranged in 23 pairs. Most of the genes in the two chromosomes of each pair are identical or almost identical with each other. However, with KFS individuals, there appears to be a reversal or inversion on part of chromosome 8.

Demographics

Approximately one out of every 42,000 people has Klippel-Feil sequence. The classic triad is seen in 52% of individuals with the syndrome. Men and women are affected equally, however, some studies have shown slightly higher numbers for women. There have been some reports of Klippel-Feil sequence being more common among infants born with **fetal alcohol syndrome** (FAS) because FAS affects bone development of the fetus. However, there is a genetic component that passes the syndrome on through the generations in a dominant **inheritance** pattern.

Signs and symptoms

The first clinical signs are the classic triad of webbed neck, low hairline, and decreased flexibility of the neck. However, the presence of abnormalities of the cervical

KEY TERMS

Degenerative disc disease—Narrowing of the disc space between the spinal bones (vertebrae).

Fetal alcohol syndrome—Syndrome characterized by distinct facial features and varying mental retardation in an infant due to impaired brain development resulting from the mother's consumption of alcohol during pregnancy.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Microtia—Small or underdeveloped ears.

Ossicles—Any of the three bones of the middle ear, including the malleus, incus, and stapes.

Radiculopathy—A bulging of disc material often irritating nearby nerve structures resulting in pain and neurologic symptoms. A clinical situation in which the radicular nerves (nerve roots) are inflamed or compressed. This compression by the bulging disc is referred to as a radiculopathy. This problem tends to occur most commonly in the neck (cervical spine) and low back (lumbar spine).

Scoliosis—An abnormal, side-to-side curvature of the spine.

Torticollis—Twisting of the neck to one side that results in abnormal carriage of the head and is usually caused by muscle spasms. Also called wryneck.

spine found with x rays is the hallmark diagnosis. Other signs and symptoms may be found, but vary from person to person.

Some patients may exhibit wryneck or Torticollis, which is a twisting of the neck to one side that results in abnormal carriage of the head. The individual may have differences between the two sides of his face, known as facial asymmetry. They may also have **scoliosis** (abnormal curves of the spine).

A variety of miscellaneous abnormalities may clinically manifest themselves in Klippel-Feil sequence. Deafness occurs in about 30% of the cases. Ear abnormalities such as very small ear lobes (microtia), or deformed bones within the ear (ossicles) may be present. Patients may even have a small or absent internal ear.

Abnormalities of the blood vessels such as a missing radial artery in the forearm may decrease the size of the thumbs (thenar hypoplasia). Anomalies of the right subclavian artery (artery under the clavicle or collar bone) have been reported as well as higher incidences of artery anomalies of the upper neck (cervical vertebrae). Anomalies of the genital areas and urinary system are also common.

Individuals diagnosed with Klippel-Feil sequence frequently have problems with cervical nerves and nerves that go from the neck to the arms and hands. Individuals can have pain that starts in their neck and travels into the arms if the nerve roots coming off of the spinal cord are irritated or pinched.

Diagnosis

Klippel-Feil sequence is usually diagnosed in early childhood or adolescence. Observing the clinical signs of having the classic triad of webbed neck, low hairline, and limited cervical ranges of motion initiates the diagnosis. When further testing is done such as x ray, the diagnosis is confirmed by the fusion of multiple cervical vertebrae.

Treatment and management

If the individual has a very mild case of Klippel-Feil sequence, then the person can lead a normal life with only minor restrictions. These restrictions, such as avoiding contact sports that would place the neck at risk, are necessary because of the instability of the cervical spine. This is due to the increased motion between the fused cervical vertebrae.

Symptoms, such as pain, that occur with the arthritis and degeneration of the joints may also result. The individuals should be treated with pain medication and possible cervical traction. If neurological symptoms occur, the treatment of choice is fusion of the symptomatic area. However, due to the severe consequences of not having the preventive surgery, surgery is still the treatment most performed.

Prognosis

There have been reports of death following minor trauma because of injuries to the spinal cord in the cervical spine. Most commonly, individuals with Klippel-Feil will develop pain. Some diseases are acquired or occur because of the increased motion of the vertebrae. Degenerative disc disease, or destruction of the cushion like disc between the vertebrae is very common. The most common findings were degenerative disc disease that affected the entire lower cervical spine. Spondylotic osteophytes, or bone spurs in the spine, form as a result of this degeneration. This laying down of new bone may lead to narrowing of the canal through which the spinal cord travels (spinal stenosis).

Surgery may prevent a dangerous and fatal accident because of the instability of the spinal cord. Pain that

originates in the neck and travels into the arms (radiculopathy) is common near the sites of the surgical fusion of vertebrae. One study found that 25% of the individuals who had surgery would have had neurological problems within ten years, therefore requiring additional surgery.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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KFS Connection Online, An online Klippel-Feil Support group. <http://members.aol.com/kfsconxpgs/links.htm>.

Jason S. Schliesser, D.C.

Knobloch syndrome *see* **Encephalocele**

Konigsmark syndrome *see* **Hereditary hearing loss and deafness**

Kowarski syndrome *see* **Pituitary dwarfism syndrome**

Krabbe disease

Definition

Krabbe disease is an inherited enzyme deficiency that leads to the loss of myelin, the substance that wraps nerve cells and speeds cell communication. Most affected individuals start to show symptoms before six months of age and have progressive loss of mental and motor function. Death occurs at an average age of 13 months. Other less common forms exist with onset in later childhood or adulthood.

Description

Myelin insulates and protects the nerves in the central and peripheral nervous system. It is essential for efficient nerve cell communication (signals) and body functions such as walking, talking, coordination, and thinking. As nerves grow, myelin is constantly being built, broken down, recycled, and rebuilt. Enzymes break down, or metabolize, fats, carbohydrates, and proteins in the body including the components of myelin.

Individuals with Krabbe disease are lacking the enzyme galactosylceramidase (GALC), which metabolizes a myelin fat component called galactosylceramide and its by-product, psychosine. Without GALC, these substances are not metabolized and accumulate in large globoid cells. For this reason, Krabbe disease is also called globoid cell leukodystrophy. Accumulation of galactosylceramide and psychosine is toxic and leads to the loss of myelin-producing cells and myelin itself. This results in impaired nerve function and the gradual loss of developmental skills such as walking and talking.

Genetic profile

Krabbe disease is an autosomal recessive disorder. Affected individuals have two nonfunctional copies of the GALC **gene**. Parents of an affected child are healthy carriers and therefore have one normal GALC gene and one nonfunctional GALC gene. When both parents are carriers, each child has a 25% chance to inherit Krabbe disease, a 50% chance to be a carrier, and a 25% chance to have two normal GALC genes. The risk is the same for males and females. Brothers and sisters of an affected child with Krabbe disease have a 66% chance of being a carrier.

KEY TERMS

Globoid cells—Large cells containing excess toxic metabolic "waste" of galactosylceramide and psychosine.

Motor function—The ability to produce body movement by complex interaction of the brain, nerves, and muscles.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

The GALC gene is located on chromosome 14. Over 70 mutations (gene alterations) known to cause Krabbe disease have been identified. One specific GALC gene deletion accounts for 45% of disease-causing mutations in those with European ancestry and 35% of disease-causing mutations in those with Mexican ancestry.

Demographics

Approximately one in every 100,000 infants born in the United States and Europe will develop Krabbe disease. A person with no family history of the condition has a one in 150 chance of being a carrier. Krabbe disease occurs in all countries and ethnic groups but no cases have been reported in the Ashkenazi Jewish population. A Druze community in Northern Israel and two Moslem Arab villages near Jerusalem have an unusually high incidence of Krabbe disease. In these areas, about one person in every six is a carrier.

Signs and symptoms

Ninety percent of individuals with Krabbe disease have the infantile type. These infants usually have normal development in the first few months of life. Before six months of age, they become irritable, stiff, and rigid. They may have trouble eating and may have seizures. Development regresses leading to loss of mental and muscle function. They also lose the ability to see and hear. In the end stages, these children usually cannot move, talk, or eat without a feeding tube.

Ten percent of individuals with Krabbe disease have juvenille or adult type. Children with juvenile type begin having symptoms between three and ten years of age. They gradually lose the ability to walk and think. They may also have paralysis and vision loss. Their symptoms usually progress slower than in the infantile type. Adult Krabbe disease has onset at any time after age 10. Symptoms are more general including weakness, difficulty walking, vision loss, and diminished mental abilities.

Diagnosis

There are many tests that can be performed on an individual with symptoms of Krabbe disease. The most specific test is done by measuring the level of GALC enzyme activity in blood cells or skin cells. A person with Krabbe disease has GALC activity levels that are zero to five percent of the normal amount. Individuals with later onset Krabbe disease may have more variable GALC activity levels. This testing is done in specialized laboratories that have experience with this disease.

The fluid of the brain and spinal cord (cerebrospinal fluid) can also be tested to measure the amount of protein. This fluid usually contains very little protein but the protein level is elevated in infantile Krabbe disease. Nerve-conduction velocity tests can be performed to measure the speed at which the nerve cells transmit their signals. Individuals with Krabbe disease will have slowed nerve conduction. Brain imaging studies such as computerized tomography (CT scan) and magnetic resonance imaging (MRI) are used to get pictures from inside the brain. These pictures will show loss of myelin in individuals with Krabbe disease.

DNA testing for GALC mutations is not generally used to make a diagnosis in someone with symptoms but it can be performed after diagnosis. If an affected person has identifiable known mutations, other family members can be offered DNA testing to find out if they are carriers. This is helpful since the GALC enzyme test is not always accurate in identifying healthy carriers of Krabbe disease.

If an unborn baby is at risk to inherit Krabbe disease, prenatal diagnosis is available. Fetal tissue can be obtained through chorionic villus sampling (CVS) or **amniocentesis**. Cells obtained from either procedure can be used to measure GALC enzyme activity levels. If both parents have identified known GALC gene mutations, DNA testing can also be performed on the fetal cells to determine if the fetus inherited one, two, or no GALC gene mutations.

Some centers offer preimplantation diagnosis if both parents have known GALC gene mutations. In-vitro fertilization (IVF) is used to create embryos in the laboratory. DNA testing is performed on one or two cells taken from the early embryo. Only embryos that did not inherit Krabbe disease are implanted into the mother's womb. This is an option for parents who want a biological child but do not wish to face the possibility of abortion of an affected pregnancy.

Treatment and management

Once a child with infantile Krabbe disease starts to show symptoms, there is little effective treatment. Supportive care can be given to keep the child as comfortable as possible and to counteract the rigid muscle tone. Medications can be given to control seizures. When a child can no longer eat normally, feeding tubes can be placed to provide nourishment.

Affected children who are diagnosed before developing symptoms (such as through prenatal diagnosis) can undergo bone marrow transplant or stem cell transplant. The goal of these procedures is to destroy the bone marrow which produces the blood and immune system cells. After the destruction of the bone marrow, cells from a healthy donor are injected. If successful, the healthy cells travel to the bone marrow and reproduce. Some children have received these transplants and had a slowing of their symptom's progression or even improvement of their symptoms. However, these procedures are not always successful and research is being done in order to reduce complications.

Scientists are also researching **gene therapy** for Krabbe disease. This involves introducing a normal GALC gene into the cells of the affected child. The goal is for the cells to integrate the new GALC gene into its DNA and copy it, producing functional GALC enzyme. This is still in research stages and is not being performed clinically.

Prognosis

Prognosis for infantile and juvenile Krabbe disease is very poor. Individuals with infantile type usually die at an average age of 13 months. Death usually occurs within a year after the child shows symptoms and is diagnosed. Children with juvenile type may survive longer after diagnosis but death usually occurs within a few years. Adult Krabbe disease is more variable and difficult to predict but death usually occurs two to seven years after diagnosis.

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United Leukodystrophy Foundation. 2304 Highland Dr., Sycamore, IL 60178. (815) 895-3211 or (800) 728-5483. Fax: (815) 895-2432. <http://www. ulf.org>.

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Amie Stanley, MS

L

Lamellar ichthyosis *see* **Ichthyosis**

Langer-Giedion syndrome

Definition

Langer-Giedion syndrome (LGS) is a rare genetic disorder characterized by skeletal abnormalities and dysmorphic (distinctive) facial features. Most people with LGS also have mental retardation.

Description

LGS affects mostly the skeletal system and facial structure. Since the features include abnormalities in the hair (tricho), nose shape (rhino), and fingers and toes (phalangeal), another name for LGS is tricho-rhino-phalangeal syndrome, type II.

Genetic profile

LGS is not usually passed through generations in a family. However, the condition is considered a contiguous-gene syndrome. This means that it is caused by the loss of functional copies of two genes near each other on chromosome 8. Research suggests that another **gene** may be involved. **Genetic counseling** is suggested for anyone considering pregnancy who has a relative with this condition.

Demographics

About 50 cases of Langer-Giedion syndrome have been reported in the literature. Males are affected three times more often than females.

Signs and symptoms

Craniofacial features associated with Langer-Giedion syndrome include a bulbous, pear-shaped nose; a small jaw; a thin upper lip; and large ears. The hair is usually sparse, and the head is small in 60% of individuals with LGS. Mild to severe mental retardation is present in 70% of people; it often affects speech more than other skills.

Skeletal features include exostoses—spiny growths on the bone—which occur before age five and usually increase in number until the skeleton matures. Compression of nerves or blood vessels, asymmetric limb growth, and limitation of movement are problems that can result from the exostoses. Scoliosis—a curvature of the spine—is found in some people, as well as thin ribs. Short stature is often seen as a result of epiphyses—cone-shaped bone ends. Longitudinal bone growth appears to be slowed. Short and/or curved fingers are common. Loose skin often occurs, but that tends to improve with age.

Features of LGS that are less commonly seen include loose joints and low muscle tone. Others are wandering eye (exotropia), droopy eyelid, widely spaced eyes, fractures in the bones, birthmarks that increase with age, hearing loss, heart or genito-urinary abnormalities, and webbing of the fingers.

Diagnosis

The criteria for diagnosis of LGS are a bulbous, pear-shaped nose, and epiphyses and exostoses. These signs are probably all related to abnormal bone growth, but researchers do not yet understand the link to mental retardation and hair abnormalities. The distinctive facial features may be recognized at birth. Changes in the epiphyses are recognizable through x ray by age three, and exostoses are visible by age five. Chromosome analysis will likely reveal an abnormality in a certain region of chromosome 8.

There are no reports of prenatal diagnosis of this condition. To provide accurate genetic counseling regarding prognosis and risk of recurrence, it is important to distinguish this condition from others that are similar to it, such as tricho-rhino-phalangeal syndrome, type 1.

KEY TERMS

Contiguous gene syndrome—A genetic syndrome caused by the deletion of two or more genes located next to each other.

Craniofacial—Relating to or involving both the head and the face.

Epiphysis—The end of long bones, usually terminating in a joint.

Exostose—An abnormal growth (benign tumor) on a bone.

Mental retardation—Significant impairment in intellectual function and adaptation in society. Usually associated with an intelligence quotient (IQ) below 70.

Philtrum—The center part of the face between the nose and lips that is usually depressed.

Short stature—Shorter than normal height, can include dwarfism.

Treatment and management

The treatment for LGS is tailored to each person. Exostoses may need to be surgically removed if they are causing problems with nerves or blood vessels. If the two leg lengths are different, corrective shoes may be helpful. Orthopedic devices such as braces or, more rarely, surgery may be indicated in severe cases of skeletal abnormality. Plastic surgery to alter specific features, such as the ears or nose, has been chosen by some people.

The risk of **cancer** at the site of the exostoses is not known but may be higher.

Special education for mentally retarded individuals is indicated. A focus on speech development may be appropriate.

Prognosis

Langer-Giedion syndrome does not alter lifespan. Complications from associated abnormalities such as mental retardation, however, can cause problems. Asymmetry of the limbs can interfere with their function and cause pain. Psychological effects due to physical abnormalities may also be experienced.

Resources

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Langer-Giedion Syndrome Association. 89 Ingham Ave., Toronto, Ontario M4K 2W8, Canada. (416) 465-3029. kinross@istar.ca.

National Institute on Deafness and Other Communication Disorders. 31 Center Dr., MSC 2320, Bethesda, MD 20814. (301) 402-0900. nidcdinfo@nidcd.nih.gov. <http://www.nidcd.nih.gov>.

WEBSITES

NORD—National Organization for Rare Diseases. <http://www.rarediseases.org>.

OMIM—Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nig.gov>.

Amy Vance, MS, CGC

Langer-Saldino syndrome *see* **Achondrogenesis**

Larsen syndrome

Definition

Larsen syndrome is an inherited condition characterized by congenital dislocation of multiple body joints along with other unusual features of the face, hands, and bones.

Description

This condition was first described in 1950 by Larsen, Schottstaedt, and Bost, who compiled information on six people with sporadic cases of Larsen syndrome.

Larsen syndrome has been called both a skeletal dysplasia (a condition caused by abnormalities of bone structure), and a hypermobility syndrome (a condition involving abnormally loose joints). It is most likely caused by inherited abnormalities of connective tissue that affect both bone and joint structure.

Present at birth are multiple dislocations of the elbows, hips, and most commonly the knees. Persons with Larsen syndrome have other distinctive physical features that can include a prominent forehead, widely spaced eyes, long cylindrical fingers, and short bones of

the hand. Sometimes present are other birth defects such as structural heart defects, cleft palate, cataracts, extra bones of the wrist, and abnormalities of the vertebrae.

Most people have moderate symptoms that can be treated, allowing for a relatively normal life span. However, a small number of babies have a severe form of the condition and die at birth.

Genetic profile

There are likely to be multiple different causes for Larsen syndrome. Both recessive and dominant patterns of **inheritance** have been described thus far.

Some cases are sporadic, meaning the affected person is the first in the family to have the condition. Many sporadic cases are though to be cause by new dominant mutations (spontaneous changes in the genetic material). A person with sporadic Larsen syndrome has a change in the genetic material that is not present in either parent but can be passed on, with 50/50 odds in each child, to his or her offspring.

Patients have been reported who have affected brothers or sisters but unaffected parents. Most of these cases probably represent a recessive form of Larsen syndrome in which a person must have two copies of a genetic change in order to be affected. The parents of a person with a recessive condition must each have one copy of the genetic change in order to have an affected child.

There are rare instances in which a person with Larsen appears to have the recessive form but then gives birth to an affected child. These cases are most likely dominant rather than recessive. It can be difficult to be certain of the inheritance pattern in some families and genetic counselors must be careful to address both forms of inheritance when discussing chances of recurrence.

The autosomal dominant form of Larsen syndrome is thought to be due to mutations in a **gene** called LAR1, on the short arm of chromosome 3. The exact structure and function of this gene is not yet known. There may be other genes responsible for a proportion of cases of dominant Larsen syndrome; however, as of 2001, no other candidate genes have been located.

Another dominantly inherited condition called Atelosteogenesis Type III (AOIII) has features which overlap with Larsen syndrome, and may, in fact, be a variant of Larsen caused by mutations in the same gene.

Demographics

Larsen syndrome is an extremely rare genetic condition that occurs in about one in every 100,000 births.

A variant of Larsen syndrome is found in high frequency on La Reunion island near East Africa. Over 40 affected children have been reported, with an incidence of 1/1500 births. This variant is thought to be recessive but the responsible gene has not yet been located.

KEY TERMS

Arthrogryposis—Abnormal joint contracture.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Clubfoot—Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

Congenital—Refers to a disorder that is present at birth.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Contrature—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Deformation—An abnormal form or position of a part of the body caused by extrinsic pressure or mechanical forces.

Epiphysis—The end of long bones, usually terminating in a joint.

Hypermobility—Unusual flexibility of the joints, allowing them to be bent or moved beyond their normal range of motion.

Joint dislocation—The displacement of a bone from its socket or normal position.

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Skeletal dysplasia—A group of syndromes consisting of abnormal prenatal bone development and growth.

Signs and symptoms

The symptoms of Larsen syndrome are widely variable from person to person and can range from lethal to very mild, even among members of the same family.

Typical characteristics at birth are multiple joint dislocations that can include hips, elbows, wrists, and knees. Babies can be born with their knees in hyperextension with their ankles and feet up by their ears, a deformation called genu recurvatum. **Clubfoot** is common and persistent flexion, or contractures, of other joints, such as the wrist and fingers, can also occur.

Persons with Larsen syndrome often have distinctive facial features. Common findings, in addition to a large forehead and wide spaced eyes, are flat cheekbones and a flat bridge of the nose, which is sometimes indented and called "saddle nose". The hands are often short but the fingers are long and lack the normal tapered ends.

Other birth defects can occur but are not present in all people. Cleft palate, cataracts, and heart defects of the valves or between the upper or lower chambers occur occasionally.

Often, babies have floppy muscle tone giving them a "rag doll" appearance. Respiratory problems are frequently seen at birth because of laxity of the trachea. Feeding and swallowing difficulties are common.

Abnormalities of the bones are frequent. Underdevelopment and abnormal shape of some of the vertebral bones can lead to problems such as **scoliosis** or kyphosis. Abnormalities of the epiphyses (centers of bone growth) can develop in childhood. Height is often reduced, and an adult height of four to five feet is not uncommon. The joints between the bones of the ear may be abnormal and may cause conductive hearing loss.

Hypermobility of joints lasts throughout life and may lead to early-onset arthritis, recurrent dislocations, and may necessitate joint replacement at an early age. Cervical spine instability is a very serious complication of Larsen syndrome as it can cause compression of the spinal cord and lead to paralysis or death.

The condition does not affect intelligence and children can expect to have normal school experiences, with the exception of physical education, which will need to be adapted to each child's needs.

Diagnosis

Larsen syndrome should be suspected in any baby having multiple joint dislocations at birth. As of 2001, there is no genetic test to confirm the diagnosis and, thus, diagnosis must be based on clinical and x ray findings. Babies suspected to have the condition warrant a complete evaluation by a medical geneticist (a physician specializing in genetic syndromes).

Larsen syndrome is sometimes misdiagnosed as another condition called arthrogryposis, which involves multiple joint contractions. Larsen syndrome can be distinguished from this and other syndromes involving joint dislocations or contractions because of the unusual constellation of features found in the face and hands. Extra bones of the wrist, often seen in Larsen syndrome, are extremely rare in other syndromes.

Some people have very mild symptoms and may not have joint dislocations or other problems at birth. The diagnosis can be missed in these people unless they are carefully evaluated.

A person with dominantly inherited Larsen syndrome has a 50% chance with each pregnancy of having a child with the same disorder. **Genetic counseling** can help couples sort out their options for parenthood. Some couples would choose to adopt rather than take the chance of an affected child, others would go ahead with a pregnancy, and others would choose to have prenatal diagnosis. The only form of prenatal diagnosis available to date is ultrasound.

Fetal ultrasound performed by a specialist at 18-20 weeks of pregnancy can sometimes reveal signs of Larsen syndrome. Knee dislocations and hyperextension, club feet, fixed flexion of elbows, wrists, and fingers, and some of the characteristic facial features can sometimes be noted by ultrasound in affected fetuses. Physical findings from ultrasound can suggest but do not confirm the diagnosis of Larsen syndrome in a fetus.

Treatment and management

Treatment will vary according to the symptoms of a particular child. Joint problems require long-term orthopedic care. Dislocations, clubfeet, and joint contractures are treated with intensive physical therapy, splints, casting, and/or surgery. Physical therapy is also important after joint surgery to build up muscles around the joint and preserve joint stability. Occupational therapy may be helpful for children with wrist and finger contractures.

Respiratory problems at birth may necessitate oxygen or assistive breathing devices. If not alleviated by medication or special feeding techniques, eating and swallowing problems may require tube feeding. Heart problems, cleft palate, and cataracts often warrant surgical correction. Special care is needed if laxity of the trachea is present because of an increased risk for respiratory problems during and after surgery.

People with chronic pain associated with hypermobile joints often can be helped by techniques taught in a pain management clinic.

Magnetic resonance imaging (MRI) of the neck is recommended in childhood to screen for cervical vertebral problems. Early diagnosis and surgical stabilization of the spine can help patients avoid paralysis and death

from spinal cord compression. Scoliosis is usually treated by bracing, or by a surgically placed metal rod. Artificial hip and knee replacements may be needed in early-to-mid adulthood because of degeneration of unstable joints.

Regular medical examinations are crucial to assess the condition of the bones, joints, spine, heart, and eyes. Hearing should be evaluated on a periodic basis, especially in children, because of the potential for conductive hearing loss. Ophthalmologic examinations are recommended periodically to screen for cataracts.

Prognosis

The effects of the syndrome vary markedly from person to person. Therefore, prognosis is based on the findings in a given individual. The usual causes of early death are either severe respiratory problems or compression of the cervical spine from vertebral instability.

If careful and consistent orthopedic treatment is initiated early, prognosis can be good, with a normal life span. Weak and unstable joints and limited range of motion from contractures may cause walking difficulties and restrict other physical activities. Contact sports and heavy lifting should be avoided as anything that puts extra strain or pressure on the joints can cause harm. Swimming is a good activity because it helps strengthen muscles without joint strain.

Resources

PERIODICALS

Becker, R., et al. "Clinical Variability of Larsen Syndrome: Diagnosis in a Father after Sonographic Detection of a Severely Affected Fetus." *Clinical Genetics* 57 (2000): 148-150.

Tongsong, T., et al. "Prenatal Sonographic Diagnosis of Larsen Syndrome." *Journal of Ultrasound Medicine* 19 (2000): 419-421.

ORGANIZATIONS

Arthritis Foundation. 1330 West Peachtree St., Atlanta, GA 30309. (800) 283-7800 or (404)965-7537. <http://www.arthritis.org>.

Scoliosis Research Society. 6300 N. River Rd., Ste 727, Rosemont, IL 60018-4226. (847)698-1627. Fax: (847) 823-0536. Goulding@aaos.org. <http://www.srs.org/>.

WEBSITES

Larsen Syndrome Resource Page. <http://www.stormloader.com/nita/ls.html>

Hypermobility Syndrome Association. <http://www.hypermobility.org/>

Barbara J. Pettersen

Late onset multiple carboxylase deficiency
see **Biotinidase deficiency**

Laurence-Moon-Bardet-Biedel syndrome
see **Bardet-Biedel syndrome**

Leber congenital amaurosis

Definition

Leber congenital amaurosis (LCA) is a group of autosomal recessive-inherited eye disorders which lead to blindness at birth or within the first few years of life. Other manifestations of the disease may include hearing loss, mental retardation, and decreased physical coordination.

Description

Vision is an important and complex sense by which the qualities of an object, such as color, shape, and size, are perceived through the detection of light. For proper vision, a critical series of biological steps must occur; if any of the steps in the process is abnormal, visual impairment or blindness may occur.

The process of vision begins with light that bounces off an object and passes through the outer coverings and lens of the eye and projects onto a layer of cells at the back of the eye called the retina. The retina contains two kinds of specialized cells types, called the rods and cones, that are responsible for sensing visual stimuli. When rods and cones are stimulated by light, impulses are conducted through the optic nerve to a region in the back of the brain known as the occipital lobe. The occipital lobe contains the visual cortex, the area of the brain that processes visual stimuli and integrates signals sent by the retina to obtain a composite image of an object.

Leber congenital amaurosis (LCA) is term for a group of inherited conditions in which the rod and cone receptors in the retina are defective or missing. Without the proper function of these specialized cells, light cannot be sensed normally.

LCA is often referred to by other names, such as: congenital absence of the rods and cones, congenital retinal blindness, congenital **retinitis pigmentosa**, Leber's congenital tapetoretinal degeneration, or Leber's congenital tapetoretinal **dysplasia**. The disorder was first described by the German ophthalmologist, Theodor Leber, in 1869, who subsequently showed that it was an inherited defect. Although similarly named, LCA should

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Braille—An alphabet represented by patterns of raised dots which may be felt with the fingertips. It is the main method of reading used by the blind today.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Electroretinography (ERG)—A diagnostic test that records electrical impulses created by the retina when light strikes it.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Occipital lobe—An anatomical subdivision, located at the back of the brain, that contains the visual cortex.

Oculo-digital reflex—A reflex causing an individual to press on their eyes with their fingers or fists.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Visual cortex—The area of the brain responsible for receiving visual stimuli from the eyes and integrating it to form a composite picture of an object.

not be confused with another disorder of sight, **Leber optic atrophy**, that was also discovered by Theodor Leber.

Genetic profile

Mutations in any one of at least six different **gene** groups may result in LCA. Each of the known genes produce proteins, which are located within the retinal rod and cone cells. These proteins participate in the detection of an incoming stimulus of light and the subsequent transmission of signals out of the retinal cells to the visual cortex of the brain. The different types of LCA and the corresponding genetic abnormality is described in the table below. These six identified mutations likely account for less than half of all diagnosed cases of LCA, and thus, there are additional mutations resulting in LCA that remain to be discovered.

LCA is a genetic condition and can be inherited or passed on in a family. The genetic defects for the disorder are all inherited as autosomal recessive traits, meaning that two mutant genes of the same group are needed to display the disease. A person who carries one mutant gene does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to their children, who must inherit the same defective gene from each parent to display the disease. Since there are different genes that are responsible for causing LCA, two individuals with different types of LCA will have an unaffected child, as it is impossible for the child to inherit two of the same type of defective genes from the parents.

Demographics

LCA has been reported to account for at least 5% of all cases of inborn blindness, but several reports suggest that is an underestimation. In 1957, scientific investigators reported that one form of LCA was responsible for 10% of blindness in Sweden. Several years later, similar rates of LCA were found in people living in the Netherlands. While this suggests that the geographical distribution of LCA is not uniform and may be higher in certain ethnic groups, a comprehensive study has never been performed.

Signs and symptoms

Because there are different types of LCA, there is considerable variation in the symptoms experienced by an affected infant. Most infants with LCA are often blind at birth or lose their sight within the first few years of life, however some people with LCA may have residual vision. In these patients, visual acuity is usually limited to the level of counting fingers or detecting hand motions or bright lights, and patients are extremely farsighted. There may be some small improvement in vision during the first decade of life as the visual system reaches maturity, but it is uncommon for children to be able to navigate without assistance or to be able to read print.

Other symptoms of LCA may include crossed eyes, sluggish pupils, rapid involuntary eye movements, unusual sensitivity to light, and the clouding of the lenses of the eyes. Many children with LCA habitually press on their eyes with their fists or fingers. This habitual pressing on the eyes is known as an oculo-digital reflex and

may represent an instinctual attempt to provide the eveloping visual cortex of the brain with a stimulus to replace the loss of normal visual stimuli. As a result of this behavior, the eyes may become thin and conical in shape and appear sunken or deep. In some cases, LCA is associated with hearing loss, **epilepsy**, decreased coordination, kidney problems, or heart abnormalities. Mental retardation may be present in approximately 20% of individuals affected with LCA.

Diagnosis

Infants are usually brought to medical attention within the first six months of life when parents note a lack of visual responsiveness and the unusual roving eye movements characteristic of the disease. As with any evidence of loss of vision, a prompt and thorough evaluation is initiated to determine the cause of the visual defect, and steps may include physical tests designed to measure brain and eye function, CT scans (a method using x rays controlled by a sophisticated computer) of the brain and eye, and even tests to look for genetic and metabolic causes of blindness.

Eye examinations of infants with LCA usually reveal a normal appearing retina. By early adolescence, however, various changes in the retinas of patients with LCA become readily apparent; blood vessels often become narrow and constricted, and a variety of color changes can also occur in the retina and its supportive tissue.

One of the most important tests in diagnosing LCA is called electroretinography (ERG). This test measures electrical impulses which are produced in the retina when light is sensed by the rod and cone cells. It is useful in distinguishing whether blindness is due to a problem in the retina versus a problem in the visual cortex of the brain. When ERG tests are performed on people with LCA, there is no recordable electrical activity arising from the eye, indicating the problem is based in the retina rather than in the brain.

Thus, an absence of activity on ERG, combined with the absence of diagnostic signs of other conditions which result in blindness, point to a diagnosis of LCA. Although several abnormal genes have been identified which are responsible for LCA, genetic analysis and prenatal diagnosis is rarely performed outside of research studies.

Treatment and management

Currently, there is no treatment for LCA, and thus, patient and family education and adaptive assistance is critical. Some people with remaining vision may benefit from vision-assistance technology such as electronic, computer-based, and optical aids, but severely visually-impaired individuals often utilize traditional resources such as canes and companion-guide dogs. Orientation and mobility training, adaptive training skills, job placement and income assistance are available through hospital physical and occupation therapy programs and various community resources. It should be noted that up to 20% of patients with LCA may have associated mental retardation and will require additional adaptive and vocational assistance.

TABLE 1

Location of genetic abnormality for specific types of Leber congenital amaurosis

Type	Abnormal	Mutant gene	Gene location
LCA1	Retinal-specific guanylate cyclase	RETGC/GUC2D	17p13.1
LCA2	Retinal pigment epithelium-specific protein	RPE65	1p31
LCA3	Unknown	Unknown	14q24
LCA4	Arlhydrocarbon-interacting protein-like 1	AIPL1	17p13.1
LCA5	Unknown	Unknown	6q11–q16
LCA due to CRX defect	Cone-rod homeobox protein	CRX	19q13.3

Most people with LCA are unable to read print and instead utilize braille, an alphabet represented by raised dots that can be felt with the fingertips. People with LCA often attend schools specially designed to meet the needs of visually-impaired students and may require modifications to their home and work environments in order to accommodate their low or absent vision. As almost all patients with LCA are legally blind, they will not be able to drive or operate heavy machinery. **Genetic counseling** may assist affected individuals with family planning.

Scientists have isolated several mutant genes that can each cause LCA. Ongoing scientific research is directed toward understanding how these genes function in the retina and toward locating the remaining genes that cause LCA. With this information, scientists can better develop a means of prevention and treatment. A dramatic example of this principle was provided in 2000, when researchers were able to restore vision in mice with LCA2. By giving oral doses of a chemical compound derived from vitamin A, the scientists were able to restore the animals' visual functions to almost normal levels after just two days. The researchers report that they will attempt the same experiments in dogs with LCA2 before trying the treatment in humans. It should be noted that LCA2 causes only 10% of the known cases of LCA, and the treatment in this experimental study does not work for other types of LCA.

Prognosis

While children born with LCA may have variable symptoms and differing levels of visual acuity, they can lead productive and healthy lives with adaptive training and assistance. In those patients who do not have associated problems with their brain, heart, or kidney, lifespan is approximately the same as the general population, otherwise the prognosis is variable and depends on the extent of the complication.

Resources

BOOKS

"Disorders of Vision" In *Nelson Textbook of Pediatrics,* edited by R. E. Behrman. Philadelphia: W. B. Saunders, 2000, pp. 1900-1928.

PERIODICALS

Dharmaraj, S. R., et al. "Mutational Analysis and Clinical Correlation in Leber Congenital Amaurosis." *Ophthalmic Genetics* 21 (September 2000): 135-150.

Gamm, D. M., and A.T. Thliveris. "Implications of Genetic Analysis in Leber Congenital Amaurosis." *Archives of Ophthalmology* 119 (March 2001): 426-427.

Lambert, S. R., A. Kriss, and D. Taylor. "Vision in Patients with Leber Congenital Amaurosis." *Archives of Ophthalmology* 11 (February 1997): 293- 294.

Perrault, I. "Leber Congenital Amaurosis." *Molecular Genetics and Metabolism* 68 (October 1999): 200-208.

ORGANIZATIONS

Foundation Fighting Blindness. Executive Plaza 1, Suite 800, 11350 McCormick Rd., Hunt Valley, MD 21031-1014. (888) 394-3937. <http://www.blindness.org>.

WEBSITES

"Entry 20400: Leber Congenital Amaurosis, Type 1." *OMIM—Online Mendelian Inheritance in Man.* <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=20400>.

Leber's Links: Leber's Congenital Amaurosis. <http://www.freeyellow.com/members4/leberslinks/index.html>.

Oren Traub, MD, PhD

Lebers hereditary optic neuropathy *see* **Lebers hereditary optic atrophy**

Lebers hereditary optic atrophy

Definition

Lebers hereditary optic atrophy is a painless loss of central vision (blurring of objects and colors appearing less vivid) that usually begins between the ages of 25 and 35 (but can occur at any age) and leads to legal blindness. Other minor problems may be present such as tremors, numbness or weakness in arms and legs, or loss of ankle reflexes. It was first described in 1871 by Theodore Leber and is the most common cause of optic atrophy.

Description

Lebers hereditary optic atrophy is also called Lebers hereditary optic neuropathy or LHON. The beginning of visual blurring in both eyes is called the acute phase of LHON. In about half the patients, both eyes are affected at the same time. In the remainder of patients, central vision is lost in one eye over a period of a few weeks, then a month or two later, the second eye is affected. Once both eyes are affected, a few weeks usually pass before the eyesight stops getting worse. Other less common patterns of central vision loss in LHON can be very sudden loss in both eyes, or very gradual loss occuring over several years. After the acute phase, there is rarely any significant change in eyesight during the remainder of the person's life. People with LHON are usually left with some peripheral vision, which is seeing around the edges, or out of the corner of the eye. This final phase is called the atrophic phase because the optic discs are atrophic (cells have wasted away) and rarely change.

The optic disc is the center part of the retina (back of the eye) and is where the clearest vision—both in detail and color—comes from. The retina is what interprets what a person sees and sends this message to their brain, along the pathway known as the optic nerve. In LHON, both the retina and the optic nerve stop working properly. The rest of the eye works normally, so that light enters the eye through the pupil (black circle in the center of the iris, the colored part of the eye) as it should. However, even though the light is focused on the retina properly, in LHON, this information isn't converted into signals for the brain to process. When a person wears prescription glasses, the purpose is to help focus light properly on the retina. In LHON, light is already focused as it should be, so glasses will not improve vision. Magnifying glasses and telescopes do help, however, because they make things look bigger. When a person looks through a magnifier or telescope they use more of their retina to see, and some undamaged cells of the retina may be able to provide some information to the brain.

Suddenly losing vision is a shock. Patients diagnosed with LHON may feel they have no useful sight left, and often, their family and friends treat them as the stereotypic blind person. In reality, LHON usually leaves an affected person with some useable vision. A variety of visual aids are available to enhance this.

KEY TERMS

Acute phase—The initial phase of LHON where visual blurring begins in both eyes, and central vision is lost.

Atrophic phase—The final phase of LHON where cells in the optic disc and optic nerve have atrophied, resulting in legal blindness. Peripheral vision remains.

Central vision—The ability to see objects located directly in front of the eye. Central vision is necessary for reading and other activities that require people to focus on objects directly in front of them.

Heteroplasmy—When all copies of mitochondrial DNA are not the same, and a mix of normal and mutated mitochondrial DNA is present.

Homoplasmy—When all copies of mitochondrial DNA are the same, or have the same mutation.

Lebers hereditary optic atrophy or Lebers hereditary optic neuropathy (LHON)—Discovered in 1871 by Theodore Leber, the painless loss of central vision in both eyes, usually occurring in the second or third decade of life, caused by a mutation in mitochondrial DNA. Other neurological problems such as tremors or loss of ankle reflexes, may also be present.

Lifetime risk—A risk which exists over a person's lifetime; a lifetime risk to develop disease means that the chance is present until the time of death.

Mitochondria—Organelles within the cell responsible for energy production.

Mitochondrial inheritance—Inheritance associated with the mitochondrial genome which is inherited exclusively from the mother.

Multiple sclerosis (MS)—A progressive degeneration of nerve cells that causes episodes of muscle weakness, dizziness, and visual disturbances, followed by periods of remission.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Ophthalmologist—A physician specializing in the medical and surgical treatment of eye disorders.

Optic disc—The region where the optic nerve joins the eye, also refered to as the blind spot.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Peripheral vision—The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

Pupil—The opening in the iris through which light enters the eye.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Genetic profile

In 60% of patients with LHON, there is a positive family history of LHON, while the remaining cases are considered sporadic (occur by chance), where only one person in the family has LHON. In 1988 it was discovered that LHON is caused by a mutation in a mitochondrial **gene**. Mitochondria are the energy producing organelles (structures) of cells. They have their own genetic material called mitochondrial DNA, which is separate from the usual genetic material contained in the center of the cell (or nucleus). Each mitochondria has several copies of its' circular DNA. DNA is the chemical that makes up genes. Genes code for certain traits, and in some cases, can code for disease. Mutations in the DNA of a mitochondria may be present in all copies (called homoplasmy), or may be present in a portion of the mitochondria's DNA (called heteroplasmy). About 15% of individuals with LHON are heteroplasmic, which means some of their mitochondrial DNA has a mutation, and some does not. This may have a bearing on the chance to develop symptoms, and on the risk of transmission.

There are three specific DNA changes or mutations that are found in the majority (90-95%) of LHON cases. The remaining LHON patients have other various mitochondrial mutations. In genetics, mutations are designated in such a way as to tell a scientist where they are located in the mitochondrial DNA and what the DNA alteration is:

- G11778A (i.e., mutation is located at position 11778; DNA change is G [guanine] to A [adenine]—a change in the base pairs that make up DNA)
- T14484C

• G3460A

Not all persons who have one of these mutations will develop LHON, since it is thought that additional genetic or environmental factors are necessary to develop central vision loss. In general, males with one of these mutations have a 40% lifetime risk to develop symptoms of LHON, while females have a 10% risk, although the actual risk varies slightly from mutation to mutation. In addition, the older a person in whom a mutation has been identified becomes without symptoms, the less likely they will lose their vision at all. If a person is going to experience vision loss from LHON, the majority of people with a mutation will express symptoms by the age of 50 years.

Environmental factors that can reduce the blood supply to the retina and optic nerve, and 'trigger' the vision loss in LHON to begin, include heavy drinking or smoking, exposure to poisonous fumes such as carbon monoxide, high levels of stress, and certain medications. A person in whom a mutation has been identified is considered more susceptible to some of these exposures and are advised not to smoke and to moderate their alcohol intake if they are asymptomatic.

The other important concept to understand in relation to mitochondrial disease is that mitochondria are only inherited from the mother. Therefore, a woman with a mitochondrial mutation (whether she has symptoms or not) will pass it to all of her offspring. Sons who inherit the mutation will not pass it to any of their children, while daughters who inherit the mutation will pass it to all of their children. This is in contrast to nuclear DNA, where half the genetic material is inherited from each parent.

Demographics

Males have LHON more often than females, however, females may develop LHON at a slightly older age and may have more severe symptoms, including a multiple sclerosis-like illness. Multiple sclerosis is a progressive degeneration of nerve cells that causes episodes of muscle weakness, dizziness, and visual disturbances, followed by remission. The onset of LHON usually occurs by 50 years if a mitochondrial DNA mutation is present, although it can present as late as the sixth or seventh decade of life.

Signs and symptoms

Symptoms of LHON include a painless sudden loss of central vision, both in visual detail and color, in both eyes over a period of weeks to months. Peripheral vision (seeing out of the corner of the eye) remains. Additional symptoms involving the neurological system may be present such as tremors, numbness or weakness in arms or legs, or loss of ankle reflexes. Symptoms vary by gender and type of mutation present. The following mutations are frequently identified and well understood:

• G11778A—the most common mutation and usually the most severe vision loss

• T14484C—usually has the best long term prognosis or outcome

• G3460A—has an intermediate presentation

Persons who have a multiple sclerosis-like illness can have any of the three mutations. This phenomena–where different mutations give different clinical outcomes–is called a genotype-phenotype correlation. The word genotype describes the specific findings in DNA, while the word phenotype is used to describe the clinical presentation.

Diagnosis

Suspicion of LHON is usually made by an ophthalmologist after a complete eye examination. **Genetic testing** for the presence/absence of mitochondrial mutations can then be performed from a small blood sample. After a symptomatic person with LHON in a family has been identified to have a mitochondrial mutation, other asymptomatic at-risk relatives can also be tested. At-risk relatives would include the affected persons' mother, siblings, and the offspring of any females found to have the mutation. Testing for asymptomatic children who are at-risk is not currently offered since no treatment is available for LHON; these individuals could opt for testing upon becoming a legal adult (i.e. reaching 18 years of age). Prenatal diagnosis for LHON is presently not available in the United States, but may be offered elsewhere. With genetic testing for LHON, it is important to remember that the presence of a mitochondrial mutation does not predict whether the condition will occur at all, the age at which it will begin, the severity, or rate of progression.

Treatment and management

There is no proven treatment available for LHON, although some studies report benefit from various vitamin therapies or other medications. Management of LHON is supportive, utilizing visual aids such as magnifiers.

Prognosis

The loss of central vision tends to remain the same (legally blind) over a lifetime once a person with LHON has reached the atrophic phase.

Resources

ORGANIZATIONS

International Foundation for Optic Nerve Disease. PO Box 777, Cornwall, NY 12518. <http://www.ifond.org>.

United Mitochondrial Diseases Foundation. PO Box 1151, Monroeville, PA 15146-1151. <http://www.umdf.org>.

WEBSITES

Leber's Optic Neuropathy. <http://www.leeder.demon.co.uk/pages/lhonhome.htm>.

Catherine L. Tesla, MS, CGC

Leigh syndrome

Definition

Leigh syndrome is a rare inherited neurometabolic disorder characterized by degeneration of the central nervous system (brain, spinal cord, and optic nerve), meaning that it gradually loses its ability to function properly.

Description

First described in 1951, Leigh syndrome usually occurs between the ages of three months and two years. The disorder worsens rapidly; the first signs may be loss of head control, poor sucking ability, and loss of previously acquired motor skills, meaning the control of particular groups of muscles. Loss of appetite, vomiting, seizures, irritability, and/or continuous crying may accompany these symptoms. As the disorder becomes worse, other symptoms such as heart problems, lack of muscle tone (hypotonia), and generalized weakness may develop, as well as lactic acidosis, a condition by which the body produces too much lactic acid. In rare cases, Leigh syndrome may begin late in adolescence or early adulthood, and in these cases, the progression of the disease is slower than the classical form.

The disorder usually occurs in three stages, the first between eight and 12 months involving vomiting and failure to thrive, the second in infancy, characterized by loss of motor ability, eye problems and respiratory irregularity. The third stage occurs between two and 10 years of age and is chracterized by hypotonia and feeding difficulties.

In most cases, Leigh syndrome is inherited as an autosomal recessive genetic trait. However, X-linked recessive, autosomal dominant, and mitochondrial **inheritance** can also occur. Several different types of genetic enzyme defects are thought to cause Leigh syndrome, meaning that the disorder may be caused by defective enzymes, the proteins made by the body to speed up the biochemical reactions required to sustain life.

Commonly known as Leigh's disease, Leigh syndrome is also known as Leigh necrotizing encephalopathy, necrotizing encephalomyelopathy of Leigh's and subacute necrotizing encephalopathy (SNE). When it occurs in adolescence and adulthood, it may be called adult-onset subacute necrotizing encephalomyelopathy.

Genetic profile

Several different types of genetic metabolic defects are thought to lead to Leigh syndrome. A deficiency of one or a number of different enzymes may be the cause.

Classic Leigh syndrome

The usual form of Leigh syndrome is inherited as an autosomal recessive genetic trait. It has been linked to a genetic defect in one of two genes known as E2 and E3, which cause either a deficiency of the enzyme pyruvate dehydrogenase, or an abnormality in other enzymes that make pyruvate dehydrogenase work. Other cases of autosomal recessive Leigh syndrome are associated with other genetic enzyme deficiencies (i.e., NADH-CoQ and Cytochrome C oxidase), although the **gene** or genes responsible for these deficiencies are not known. All of these different genetic defects seem to have a common effect on the central nervous system.

In autosomal recessive inheritance, a single abnormal gene on one of the autosomal **chromosomes** (one of the first 22 "non-sex" chromosomes) from both parents can cause the disease. Both of the parents must be carriers in order for the child to inherit the disease and neither of the parents has the disease (since it is recessive).

A child whose parents are carriers of the disease has a 25% chance of having the disease; a 50% chance of being a carrier of the disease, meaning that he is not affected by the disease, and a 25% chance of receiving both normal genes, one from each parent, and being genetically normal for that particular trait.

X-linked Leigh syndrome

Evidence also exists for an X-linked recessive form of Leigh syndrome, which has been linked to a specific defect in a gene called E1-alpha, a part of the enzyme pyruvate dehydrogenase.

X-linked recessive disorders are conditions that are coded on the X chromosome. All humans have two chromosomes that determine their gender: females have XX, males have XY. X-linked recessive, also called sex-linked, inheritance affects the genes located on the X

chromosome. It occurs when an unaffected mother carries a disease-causing gene on at least one of her X chromosomes. Because females have two X chromosomes, they are usually unaffected carriers. The X chromosome that does not have the disease-causing gene compensates for the X chromosome that does. Generally for a woman to have symptoms of the disorder, both X chromosomes would have the disease-causing gene. That is why women are less likely to show such symptoms than males.

If a mother has a female child, the child has a 50% chance of inheriting the disease gene and being a carrier who can pass the disease gene on to her sons. On the other hand, if a mother has a male child, he has a 50% chance of inheriting the disease-causing gene because he has only one X chromosome. If a male inherits an X-linked recessive disorder, he is affected. All of his daughters will also be carriers.

Mitochondrial Leigh syndrome

Evidence also exists that Leigh syndrome may be inherited in some cases from the mother as a **DNA** mutation inside mitochondria. Hundreds of tiny mitochondria are contained in every human cell. They control the production of cellular energy and carry the genetic code for this process inside their own special DNA, called mtDNA. The mtDNA instructions from the father are carried by sperm cells, and during fertilization, these instructions break off from the sperm cell and are lost. All human mtDNA, therefore comes from the mother. The specific mtDNA defect that is thought to be responsible for some cases of Leigh syndrome, mtDNA nt 8993, is associated with the ATPase 6 gene. An affected mother passes it along to all of her children, but only the daughters will pass the mutation onto the next generation.

When mutations occur on mtDNA, the resulting genes may outnumber the normal ones. And until mutations are present in a significant percentage of the mitochondria, symptoms may not occur. Uneven distribution of normal and mutant mtDNA in different tissues of the body means that different organ systems in individuals from the same family may be affected, and a variety of symptoms may result in affected family members.

Adult–onset Leigh syndrome

In cases of adult-onset Leigh syndrome, the disorder may be inherited in yet another way, as an autosomal dominant genetic trait. In autosomal dominant inheritance, a single abnormal gene on one of the autosomal chromosomes (one of the first 22 "non-sex" chromosomes) from either parent can cause the disease. One of the parents will have the disease (since it is dominant) and will be the carrier. Only one parent needs to be a carrier in order for the child to inherit the disease. A child who has one parent with the disease has a 50% chance of also having the disease.

Demographics

Leigh syndrome is very rare. It is thought that the classic form of the disorder accounts for approximately 80% of cases and affects males and females in equal numbers. In both X-linked Leigh syndrome and adult-onset Leigh syndrome, almost twice as many males as females are affected. In adult-onset cases, progression of the disease is slower than the classical form.

Signs and symptoms

The symptoms of developmental delay, hypotonia, and lactic acidosis are present in almost all cases of Leigh syndrome. Other symptoms that may occur with the disorder are:

- Respiratory: Hyperventilation, breathing arrest (apnea), shortness of breath (dyspnea), respiratory failure. Respiratory disturbance may occur in as many as 70% of cases.
- Neurological: Muscle weakness, clumsiness, shaking, failure of muscular coordination (ataxia).
- Ocular: Abnormal eye movements, sluggish pupils, blindness.
- Cardiovascular: heart disease and malformation.
- Seizures may also occur.

Diagnosis

The diagnosis of Leigh syndrome is usually made by clinical evaluation and a variety of tests.

Advanced imaging techniques

The main body part affected is the nerve cells (gray matter) of the brain with areas of dead nerve cells (necrosis) and cell multiplication (capillary proliferation) in the lowest part of the brain (brain stem). A CT scan or magnetic resonance imaging MRI of the brain may reveal these abnormalities. Also, cysts may be present in the outer portion of the brain (cerebral cortex).

Laboratory testing

Biochemical findings are high levels of pyruvate and lactate in the blood and slightly low sugar (glucose) levels in the blood and cerebrospinal fluid (CSF), a clear fluid that bathes the brain and spinal cord. Laboratory tests may reveal high levels of acidic waste products in the blood, indicative of lactic acidosis as well as high lev-

KEY TERMS

Apnea—An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

Asymmetric septal hypertrophy—A condition in which the septum (the wall that separates the atria of the heart) is abnormally excessively thickened. In microscopic examination, normal alignment of muscle cells is absent (myocardial disarray).

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Central nervous system (CNS)—In humans, the central nervous system is composed of the brain, the cranial nerves and the spinal cord. It is responsible for the coordination and control of all body activities.

Degenerative disorder—A disorder by which the body or a part of the body gradually loses its ability to fucntion.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Hypertrophic cardiomyopathy—A condition in which the muscle of the heart is abnormally excessively thickened. In microscopic examination, normal alignment of muscle cells is absent (myocardial disarray).

Hypotonia—Reduced or diminished muscle tone.

Lactic acidosis—A condition characterized by the accumulation of lactic acid in bodily tissues. The cells of the body make lactic acid when they use sugar as energy. If too much of this acid is produced, the person starts feeling ill with symptoms such as stomach pain, vomiting, and rapid breathing.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Mitochondria—Organelles within the cell responsible for energy production.

Motor skills disorder—A disorder that affects motor coordination or its development, and the control of particular groups of muscles that perform activities.

Necrosis—Death of a portion of tissue differentially affected by disease or injury.

Neurometabolic disorder—Any disorder or condition that affects both the central nervous system (CNS) and the metabolism of the body.

els of pyruvate and alanine. The enzyme pyruvate carboxylase may be absent from the liver. An inhibitor of thiamine triphosphate (TTP) production may be present in the blood and urine of affected individuals. Blood glucose may be somewhat lower than normal. Some children with the disorder may have detectable deficiencies of the enzymes pyruvate dehydrogenase complex or cytochrome C oxidase.

Related disorders

Symptoms of other disorders are very similar to those of Leigh syndrome, and comparisons may be useful to distinguish between them. These disorders are:

- Wernicke encephalopathy
- Kufs disease
- Batten disease
- Tay-Sachs disease
- Sandhoff disease
- Niemann-Pick disease
- Alpers disease

Prenatal testing

Genetic counseling may be of benefit for families with a history of Leigh syndrome. Prenatal testing is available to assist in prenatal diagnosis. Prior testing of family members is usually necessary for prenatal testing.

Either chorionic villus sampling (CVS) or **amniocentesis** may be performed for prenatal testing. CVS is a procedure to obtain chorionic villi tissue for testing. Examination of fetal tissue can reveal information about the changes that lead to Leigh syndrome. Chorionic villus sampling can be performed at 10–12 weeks pregnancy.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus, into the amniotic sac, and withdrawing a small amount of amniotic fluid. DNA can be extracted from the fetal cells contained in the amniotic fluid and tested. Amniocentesis is performed at 15–18 weeks pregnancy.

Tissue obtained from CVS or in amniotic fluid that shows evidence of the genetic abnormalities responsible for Leigh syndrome confirms the diagnostic. Other forms of prenatal testing may be available for Leigh syndrome.

Treatment and management

The most common treatment for the disorder is the prescription of thiamine or vitamin B_1. This may result in a temporary improvement of the symptoms and slightly slow the progress of the disease.

Patients lacking the pyruvate dehydrogenase enzyme complex may benefit from a high-fat, low-carbohydrate diet.

To treat lactic acidosis, oral sodium bicarbonate or sodium citrate may also be prescribed. To control severe lactic acidosis, intravenous infusion of tris-hydroxymethyl aminomethane (THAM) may be beneficial. Both treatments help reduce abnormally high acid levels in the blood and the accumulation of lactic acid in the brain.

If eye problems occur, the individual with Leigh syndrome may benefit from treatment from an ophthamologist.

Treatment should also include assistance with locating support resources for the family and the individual with Leigh syndrome.

Prognosis

Prognosis for individuals with classical Leigh syndrome is poor. Death usually occurs within a few years, although patients may live to be 6 or 7 years of age. Some patients have survived to the mid-teenage years. Children who survive the first episode of the disease may not fully recover physically and neurologically. In addition, they are likely to face successive bouts of devastating illness that ultimately cause death.

Resources

BOOKS

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ORGANIZATIONS

Arc (a National Organization on Mental Retardation). 1010 Wayne Ave., Suite 650, Silver Spring, MD 20910. (800) 433-5255. <http://www.thearclink.org>.

Association for Neuro-Metabolic Disorders. 5223 Brookfield Lane, Sylvania, OH 43560-1809. (419) 885-1497.

Children Living with Inherited Metabolic Diseases. The Quadrangle, Crewe Hall, Weston Rd., Crewe, Cheshire, CW1-6UR. UK 127 025 0221. Fax: 0870-7700-327. <http://www.climb.org.uk>.

Children's Brain Disease Foundation. 350 Parnassus Ave., Suite 900, San Francisco, CA 94117. (415) 566-5402.

Epilepsy Foundation of America. 4351 Garden City Dr., Suite 406, Landover, MD 20785-2267. (301) 459-3700 or (800) 332-1000. <http://www.epilepsyfoundation.org>.

Lactic Acidosis Support Trust. 1A Whitley Close, Middlewich, Cheshire, CW10 0NQ. UK (016) 068-37198.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

United Mitochondrial Disease Foundation. PO Box 1151, Monroeville, PA 15146-1151. (412) 793-8077. Fax: (412) 793-6477. <http://www.umdf.org>.

WEBSITES

Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?db=OMIM>.

Jennifer F. Wilson, MS

LEOPARD syndrome *see* **Multiple lentigines syndrome**

Leprechaunism *see* **Donohue syndrome**

Leri-Weill dyschondrosteosis

Definition

Leri-Weill dyschondrosteosis (LWD) is a rare form of dwarfism. It is characterized by short forearms and lower legs as well as a certain arm-bone abnormality (Madelung deformity).

Description

LWD was first described by A. Leri and J. Weill in 1929. Other names for LWD include Leri-Weill syndrome (LWS), dyschondrosteosis (DCO), and Madelung deformity.

Genetic profile

LWD appears to be caused by several genetic factors. Many forms of LWD are caused by a mutation (change) in a **gene** called SHOX (for "short stature homeo box" gene). SHOX is located on the X chromosome. In the cases of LWD in which a specific mutation or change cannot be found in the SHOX gene, another gene may be responsible for the problems in bone devel-

opment. The involvement of another gene or some other factor would not be surprising, as a person's height is determined by the interaction of many genes and environmental factors.

Leri-Weill dyschondrosteosis can appear in an individual but not be found in his or her parents. A new, isolated type of LWD is called denovo LWD. A person with denovo LWD has a 50% chance of having children with the syndrome.

Family members with the syndrome can be affected very differently. For example, some family members may have proportional dwarfism, with no visible arm-bone abnormality, while other family members may have very short (mesomelic) arms and legs and severe Madelung arm-bone abnormality. Such differences in physical findings within the same family are known as intrafamilial variability.

Studies in 1998 and 1999 suggested that another form of severe dwarfism, Langer mesomelic **dysplasia**, is the result of inheriting two copies of the mutated gene that causes LWD. Langer mesomelic dysplasia is characterized by extremely short stature along with underdeveloped or missing arm bones.

Demographics

The ethnic origins of individuals affected by LWD are varied. LWD does not appear to be more common in any specific country.

Signs and symptoms

Most individuals affected by Leri-Weill dyschrondrosteosis have short stature based on their shortened lower legs and forearms, normal head size, and Madelung deformity. One recent study found that some males have overdeveloped muscles (or muscular hypertrophy). Depending on the individual, LWD can result in severe to very mild symptoms (variable expression). Females affected by LWD tend to have the more severe effects of LWD.

Some individuals with LWD have symptoms not part of the LWD features. These features, such as mental retardation and skin disorders, are believed to be caused by abnormalities in genes close to the mutated SHOX gene. Individuals with other symptoms as well as LWD are said to be affected by an Xp22.3 contiguous gene syndrome. The name refers to a syndrome caused by the deletion or incorrect working of several genes found side-by-side on the X chromosome.

Diagnosis

Diagnosis of LWD is usually made from physical examination by a medical geneticist, and by studies of x rays of the legs and arms. Madelung deformity of the arms is generally not visible in children through physical exam, but the first signs of the abnormality, such as bowing of the forearm bone, can be identified by x ray between ages two and five years.

Although one gene has been found to cause LWD, diagnostic **genetic testing** in affected individuals or in fetuses is not available in 2001.

KEY TERMS

Madelung's deformity—A forearm bone malformation characterized by a short forearm, arched or bow shaped radius, and dislocation of the ulna.

Mesomelia—Shortness of the portion of arm connecting the elbow to the wrist or forearm.

Treatment and management

At this time there is no specific therapy that removes, cures, or repairs all signs of the disorder. Some progress in increasing height has been made by growth hormone (GH) supplementation in affected children. However, this treatment causes disproportionate growth, with longer arms and trunk and shorter legs.

Prognosis

The severity of effects of LWD varies widely, so prognoses for people with the syndrome also vary. Severe Madelung deformity may require surgery. However, individuals with LWD have an excellent prognosis, and most have normal lives.

Resources

BOOKS

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Rieser, Patricia, and Heino F. L. Mayer-Bahlburg. *Short & Okay: A Guide for Parents of Short Children.* Human Growth Foundation.

ORGANIZATIONS

Human Growth Foundation. 997 Glen Cove Ave., Glen Head, NY 11545. (800) 451-6434. Fax: (516) 671-4055. <http://www. hgf1@hgfound.org>.

International Center for Skeletal Dysplasia. Saint Joseph's Hospital, 7620 York Rd., Towson, MD 21204. (410) 337-1250.

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408. (806) 737-8186 or (888) LPA-2001. lpadatabase@juno.com. <http://www.lpaonline .org>.

MAGIC Foundation for Children's Growth. 1327 N. Harlem Ave., Oak Park, IL 60302. (708) 383-0808 or (800) 362-4423. Fax: (708) 383-0899. mary@magicfoundation.org. <http://www.magicfoundation.org/ghd.html>.

WEBSITES

"Entry 312865: Short Stature Homeo Box; SHOX." *OMIM—Online Mendelian Inheritance of Man.* <http://www.ncbi.nlm.nih.gov:80/entrez/dispomim.cgi?id=312865>.

Family Village. <http://www.familyvillage.wisc.edu/index.html>

Dawn A. Jacob, MS

Lesch-Nyhan syndrome

Definition

Lesch-Nyhan syndrome is a rare genetic disorder that affects males. Males with this syndrome develop physical handicaps, mental retardation, and kidney problems. It is caused by a total absence of an enzyme. Self injury is a classic feature of this genetic disease.

Description

Lesch-Nyhan syndrome was first described in 1964 by Dr. Michael Lesch and Dr. William Nyhan. The syndrome is caused by a severe change (mutation) in the HPRT **gene**. This gene is responsible for the production of the enzyme called hypoxanthine-guanine phosphoribosyltransferase (HPRT). HPRT catalyzes a reaction that is necessary to prevent the buildup of uric acid. A severe mutation in the HPRT gene leads to an absence of HPRT enzyme activity which, in turn, leads to markedly elevated uric acid levels in the blood (hyperuricemia). This buildup of uric acid is toxic to the body and is related to the symptoms associated with the disease. Absence of the HPRT enzyme activity is also thought to alter the chemistry of certain parts of the brain, such as the basal ganglia, affecting neurotransmitters (chemicals used for communication between nerve cells), acids, and other chemicals. This change in the nervous system is also related to the symptoms associated with Lesch-Nyhan syndrome.

Males with Lesch-Nyhan syndrome develop neurologic problems during infancy. Infants with Lesch-Nyhan syndrome have weak muscle tone (hypotonia) and are unable to develop normally. Affected males develop uncontrollable writhing movements (athetosis) and muscle stiffness (spasticity) over time. Lack of speech is also a common feature of Lesch-Nyhan syndrome. The most dramatic symptom of Lesch-Nyhan syndrome is the compulsive self-injury seen in 85% of affected males. This self injury involves the biting of their own lips, tongue, and finger tips, as well as head banging. This behavior leads to serious injury and scarring.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Athetosis—A condition marked by slow, writhing, involuntary muscle movements.

Basal ganglia—A section of the brain responsible for smooth muscle movement.

Chorea—Involuntary, rapid, jerky movements.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

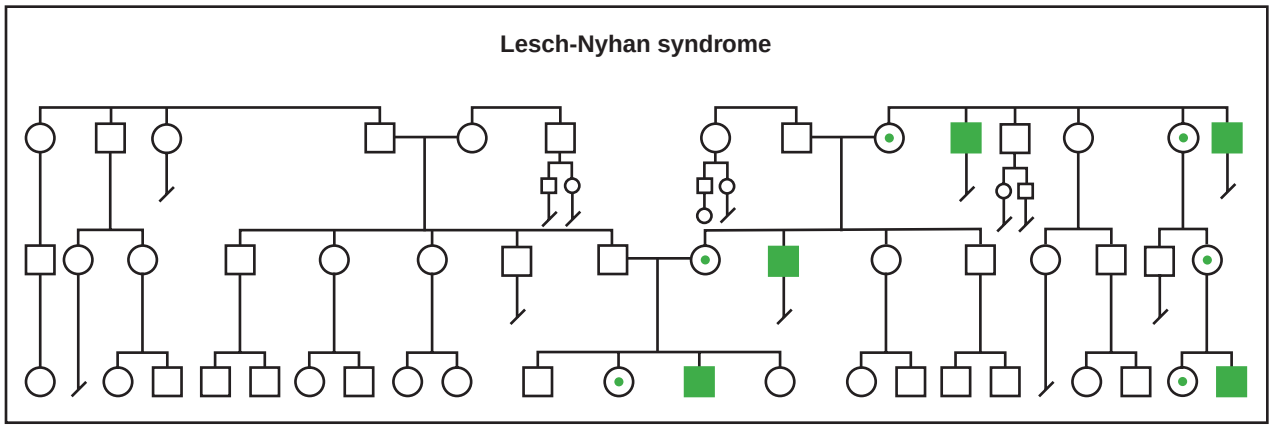
Neurotransmitter—Chemical in the brain that transmits information from one nerve cell to another.

Palsy—Uncontrollable tremors.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Genetic profile

Severe changes (mutations) in the HPRT gene completely halt the activity of the enzyme HPRT. There have been many different severe mutations identified in the HPRT gene. These mutations may be different within



(Gale Group)

families. Since the HPRT gene is located on the X chromosome, Lesch-Nyhan syndrome is considered an X-linked disorder. This means that it only affects males.

A person's sex is determined by their **chromosomes**. Males have one X chromosome and one Y chromosome. Females, on the other hand, have two X chromosomes. Males who possess a severe mutation in their HPRT gene will develop Lesch-Nyhan syndrome. Females who possess a severe mutation in their HPRT gene will not; they are considered carriers. This is because females have another X chromosome without the mutation that prevents them from getting this disease. If a woman is a carrier, she has a 50% risk with each pregnancy to pass on her X chromosome with the mutation. Therefore, with every male pregnancy she has a 50% risk to have an affected son, and with every female pregnancy she has a 50% risk to have a daughter who is a carrier.

Demographics

Lesch-Nyhan syndrome affects approximately one in 380,000 live births. It occurs evenly among races. Almost always, only male children are affected. Women carriers usually do not have any symptoms. Women carriers can occasionally develop inflammation of the joints (gout)as they get older.

Signs and symptoms

At birth, males with Lesch-Nyhan syndrome appear completely normal. Development is usually normal for the first few months. Symptoms develop between three to six months of age. Sand-like crystals of uric acid in the diapers may be one of the first symptoms of the disease. The baby may be unusually irritable. Typically, the first sign of nervous system impairment is the inability to lift their head or sit up at an appropriate age. Many patients with Lesch-Nyhan will never learn to walk. By the end of the first year, writhing motions (athetosis), and spasmodic movements of the limbs and facial muscles (chorea) are clear evidence of defective motor development.

The compulsive self-injury associated with Lesch-Nyhan syndrome begins, on average, at three years. The self-injury begins with biting of the lips and tongue. As the disease progresses, affected individuals frequently develop finger biting and head banging. The self-injury can increase during times of stress.

Males with Lesch-Nyhan disease may also develop kidney damage due to kidney stones. Swollen and tender joints (gout) is another common problem.

Diagnosis

The diagnosis of Lesch-Nyhan syndrome is based initially on the distinctive pattern of symptoms. Measuring the amount of uric acid in a person's blood or urine can not definitively diagnose Lesch-Nyhan syndrome. It is diagnosed by measuring the activity of the HPRT enzyme through a blood test. When the activity of the enzyme is very low it is diagnostic of Lesch-Nyhan syndrome. It can also be diagnosed by DNA testing. This is also a blood test. DNA testing checks for changes (mutations) in the HPRT gene. Results from DNA testing are helpful in making the diagnosis and also if the family is interested in prenatal testing for future pregnancies.

Prenatal diagnosis is possible by DNA testing of fetal tissue drawn by **amniocentesis** or chorionic villus sampling (CVS). Fetuses should be tested if the mother is a carrier of a change (mutation) in her HPRT gene. A woman is at risk of being a carrier if she has a son with Lesch-Nyhan syndrome or someone in her family has

Lesch-Nyhan syndrome. Any woman at risk of being a carrier should have DNA testing through a blood test.

Treatment and management

There are no known treatments for the neurological defects of Lesch-Nyhan. The medication Allopurinol can lower blood uric acid levels. This medication does not correct many of the symptoms. Some patients with Lesch-Nyhan syndrome have their teeth removed to prevent self-injury. Restraints are recommended to reduce self-destructive behaviors.

Prognosis

With strong supportive care, infants born with Lesch-Nyhan can live into adulthood with symptoms continuing throughout life.

At present, there are no preventive measures for Lesch-Nyhan syndrome. However, recent studies have indicated that this genetic disorder may be a good candidate for treatment with gene replacement therapy. Unfortunately, the technology necessary to implement this therapy has not yet been perfected.

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Visser, J.E., et al. "Lesch-Nyhan Disease and the Basal Ganglia." *Brain Research Reviews* (November 1999): 450–469.

ORGANIZATIONS

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

International Lesch-Nyhan Disease Association. 114 Winchester Way, Shamong, NJ 08088-9398. (215) 677-4206.

Lesch-Nyhan Syndrome Registry. New York University School of Medicine, Department of Psychiatry, 550 First Ave., New York, NY 10012. (212) 263-6458.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

GeneClinics <http://www.geneclinics.org/profiles/lns/details.html>.

Pediatric Database(PEDBASE) <http://www.icondata.com/health/pedbase/files/LESCH-NY.HTM>.

Holly Ann Ishmael, MS, CGC

Leukodystrophy

Definition

Leukodystrophy describes a collection of about 15 rare **genetic disorders** that effect the brain, spinal cord and peripheral nerves. It is characterized by imperfect growth or development of the white matter covering nerve fibers in the brain.

Description

Leukodystrophy comes from the Greek words *leuko* meaning white (referring to the white matter of the nervous system) and *dystrophy* meaning imperfect growth or development. The white matter is called the myelin sheath and is an extremely complex substance composed of at least 10, and probably more, chemicals. The myelin sheath protects the axon (a long and single-nerve cell process that acts as a wire to conduct impulses away from the cell body), much the way insulation does to an electric wire.

Each type of leukodystrophy affects one of these chemicals. Leukodystrophies covered in this essay are Alexander's disease, childhood ataxia with central nervous system hypomyelination (CACH), also known as vanishing white matter disease, cerebralautosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebrotendinous xanthomatosis (CTX), metachromatic leukodystrophy, ovarioleukodystrophy syndrome, and Van der Knapp syndrome, also called vacuolating leukodystrophy with subcortical cysts.

Leukodystrophies covered as separate entries in this encyclopedia are adrenoleukodystrophy (ALD)/adrenomyeloneuropathy (AMN), Aicardi-Goutieres syndrome, **canavan disease** (spongy degeneration), **Krabbe disease** (globoid cell leukodystrophy), neonatal adrenoleukodystrophy, **Pelizaeus-Merzbacher disease** (X-linked spastic paraplegia), **Refsum disease**, and **Zellweger syndrome**.

Genetic profile

Genes are the blueprint for the human body that directs the development of cells and tissue. Mutations in

some genes can cause genetic disorders such as leukodystrophy. Every cell in the body has 23 pairs of **chromosomes**, 22 pairs of which are called autosomes and contain two copies of individual genes. The 23rd pair of chromosomes is called the sex chromosome because it determines a person's sex. Males have an X and a Y chromosome while females have two X chromosomes.

All of the leukodystrophies discussed in this article have an autosomal recessive pattern of **inheritance** that affects males and females. People with only one abnormal **gene** are carriers but since the gene is recessive, they do not have the disorder. Their children will be carriers of the disorder but not show symptoms of the disease. Both parents must have one of the abnormal genes for a child to have symptoms of an autosomal recessive leukodystrophy. When both parents have the abnormal gene, there is a 25% chance each child will inherit both abnormal genes and have the disease. There is a 50% chance each child will inherit one abnormal gene and become a carrier of the disorder but not have the disease itself. There is a 25% chance each child will inherit neither abnormal gene and not have the disease nor be a carrier.

KEY TERMS

Arteriopathy—Damage to blood vessels.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Bile acids—Steroid acids such as cholic acid that occur in bile, an alkaline fluid secreted by the liver and passed into a part of the small intestine where it aids in absorption of fats.

Bile alcohol—A steroid acid with an alcohol group attached.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

Hypomyelination—The death of myelin on a nerve or nerves.

Ischemic attack—A period of decreased or no blood flow.

Leukoencephalopathy—Any of various diseases, including leukodystrophies, affecting the brain's white matter.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Subcortical infarcts—Obstruction of nerve centers below the cerebral cortex of the brain.

Demographics

All of the leukodystrophies discussed here appear to affect all racial and ethnic groups and all geographic populations. However, metachromatic leukodystrophy has been found in a higher frequency in highly inbred groups, such as the Habbanite Jewish population. Van der Knapp syndrome has a high prevalence among Turkish and Asian-Indian people.

Signs and symptoms

The most common signs seen in most leukodystrophies include gradual changes in an infant or child who previously appeared healthy. These changes may appear in body tone, movements, gait, speech, the ability to eat, hearing, vision, behavior, and memory. Specific signs and symptoms for individual leukodystrophies include:

- Metachromatic, with the most common and most severe form occurring between the ages of six months and two years with symptoms such as irritability, decreased muscle tone, muscle wasting, and difficulty learning to walk and talk. Onset symptoms in older children and adults include deterioration of intellectual performance, and behavioral or psychiatric problems. Blindness, seizures, and paralysis occur as the disease progresses.
- Alexander's disease, which usually begins in infancy (six to 24 months of age) and affects mostly males. Initial signs are physical and mental retardation and as the disease progresses, enlargement of the brain and head, spasticity, and seizures. In children and adults, symptoms are the same but occur less frequently and progress more slowly.
- CACH is usually diagnosed in infancy and initial symptoms include motor and speech difficulties that progressively worsen. Later symptoms include difficulty swallowing, seizures, and coma.
- CADASIL can be diagnosed in children and adults but usually shows up at around age 45. The initial symptom is usually migraine headaches, followed in about 10 years by ischemic attacks and small strokes followed by mood disturbances and **dementia**. **Epilepsy** sometimes occurs.
- CTX may present initial symptoms of cataracts, mild mental retardation, fatty tumors (called xanthomas) in

tendons, especially the Achilles tendon or heel cord. Later symptoms include seizures, emotional or psychiatric disturbances, and impaired motion or muscle movement.

- Ovarioleukodystrophy syndrome usually has onset symptoms of walking difficulties and/or mental retardation.
- Van der Knapp syndrome can have onset at or shortly after birth with the symptom of an extremely enlarged head. But onset usually occurs between ages four and five with initial symptoms of cerebella ataxia followed by spasticity. Later symptoms include mental slowing and learning problems and sometimes epileptic seizures and severe walking impairment.

Diagnosis

Leukodystrophies are occasionally misdiagnosed as **muscular dystrophy**, since they all are neurological disorders involving white matter. **Genetic testing** is usually in order for all leukodystrophies except Alexander's disease and Van der Knapp syndrome for which the specific genetic abnormalities are unknown. A nerve conduction velocity (NCV) test is sometimes used to evaluate nerve damage in people with metachromatic leukodystrophy. The NCV test sends small electrical shocks through one end of a nerve. The time it takes to travel to the other end of the nerve is measured to help determine the severity of nerve damage. Diagnosis of CTX is made by measuring the levels of bile alcohol in the blood or urine, or of cholestanol in the blood. Cholestanol is similar chemically to cholesterol but can be distinguished from it by special chemical tests. MLD and Van der Knapp syndrome diagnosis are usually made by a brain imaging scan called magnetic resonance imaging (MRI). A series of biochemical tests is sometimes used to diagnose MLD.

Treatment and management

With the exception of CTX, none of the leukodystrophies covered here are treatable. In some of the disorders, specific symptoms can be treated. For example some infections associated with MLD, such as pneumonia, can be treated with antibiotics. In ovarioleukodystrophy syndrome, ovarian insufficiency can be treated with hormone replacement therapy. But there are no treatments available for most of the conditions associated with leukodystrophies, such as mental retardation, dementia, deterioration of speech, vision, and mobility, and degeneration of myelin (white matter). In CTX, administration of certain bile acids, especially chenodeoxycholic acid, can prevent further progression of the disorder and in some cases may bring improvement.

Prognosis

The prognosis varies between leukodystrophy types but overall, most people with leukodystrophy can expect a shortened life span. Infants with Alexander's disease generally do not live past the age of five or six. Infants with metachromatic leukodystrophy (MLD) usually do not live past age 10. In children and adults, Alexander's disease and MLD progress more slowly but life expectancy is still shortened. Life expectancy with CACH is also shortened, with few people living beyond age 40 years. CADASIL progresses slowly but death occurs on average about 21–22 years after onset of symptoms. Life expectancy is closer to normal with CTX provided it is diagnosed and treated early. Ovarioleukodystrophy is a relatively newly identified disorder and there is not enough information available to make a prognosis of life expectancy, other than to say it is probably reduced. The average life expectancy is also unknown for Van der Knapp syndrome; several patients have died in their 20s but others are still alive in their 40s.

A number of government agencies and private foundations are currently funding research into many of the leukodystrophies, including identifying the cause of individual disorders, developing therapies to prevent disease progression, and to prevent onset of disease. However, little research is being done on therapies to repair damage already done by the disorders, or of restoring functions lost because of the disorders, according to The Myelin Project, a private research foundation.

Resources

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ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

United Leukodystrophy Foundation. 2304 Highland Dr., Sycamore, IL 60178. (815) 895-3211 or (800) 728-5483. Fax: (815) 895-2432. <http://www. ulf.org>.

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Ken R. Wells

Li-Fraumeni syndrome

Definition

Li-Fraumeni syndrome (LFS) is a hereditary condition in which individuals have an increased risk for developing certain kinds of tumors. The characteristic tumors of LFS are adrenocortical carcinoma, **breast cancer**, brain cancer, leukemia and sarcoma. Li-Fraumeni syndrome has previously been known as the sarcoma, breast, leukemia and adrenal gland (SBLA) syndrome.

Description

Li-Fraumeni syndrome is an inherited condition that is associated with a significantly increased risk for developing certain kinds of cancer. It is classified as a hereditary cancer syndrome and was first described in 1969 by two physicians, Dr. Li and Dr. Fraumeni. Hereditary cancer syndromes typically result in multiple family members developing cancer, in family members developing the same kind(s) of cancer, in family members developing cancer at a young age, and in family members developing more than one primary cancer. In contrast, most people who develop cancer are diagnosed later in life, such as in their sixties and seventies, and do not have multiple close family members, such as a parent and/or siblings, who have developed the same kind of cancer.

Five cancers are characteristic of LFS. These five cancers are adrenocortical carcinoma, breast cancer, brain cancer, leukemia and sarcoma. Other types of cancer such as melanoma, colon cancer and **stomach cancer** have been seen in families with LFS, but as of 2001, it is not certain whether these tumors are truly a part of LFS. A brief description of the five characteristic cancers follows.

Adrenocortical carcinoma is a rare cancer affecting a specific part of the adrenal gland called the adrenal cortex. There are two adrenal glands and each one sits on the upper part of a kidney. Adrenal glands produce hormones and if a cancer is present, more hormones may be produced resulting in symptoms. In LFS, adrenocortical carcinomas typically develop in childhood.

Brain cancer refers to a tumor developing in the brain. There are different kinds of tumors that may develop in the brain; the type depends upon the part of the brain involved. The brain tumors that occur in LFS tend to develop in young adulthood although they may develop at any age.

Breast cancer is a cancer affecting the breast, and in LFS, women are often diagnosed with breast cancer in their twenties, thirties, and forties. Although breast cancer in men is rare, it does occur both within families with LFS and in the general population.

Leukemia refers to cancer of the blood. There are more than one type of leukemia; the type depends upon the kind of blood cell involved and whether the cancer is fast (acute) or slow (chronic) growing. Overall, acute lymphocytic leukemia (ALL) is the most common leukemia in children and acute myelogenous leukemia (AML) is common in young adults. Chronic myelogenous leukemia (CML) is a common leukemia in older individuals. Li-Fraumeni syndrome is typically associated with acute leukemias and are most often diagnosed in children, adolescents and young adults.

Sarcoma refers to a soft-tissue tumor, meaning that the tumor has developed in bone, muscle, or connective tissue. Osteosarcoma refers to a sarcoma that has developed in the bone. Rhabdomyosarcoma is a sarcoma that has developed in the muscle. Both of these sarcomas are associated with LFS and typically are diagnosed in children and in adults before the age of 35 years. A third type of sarcoma, Ewing's sarcoma, is another type sarcoma arising in bone, but it is not associated with LFS.

An individual inheriting the familial LFS **gene** alteration has a significantly increased risk for developing one of the five characteristic cancers in his/her lifetime. This risk is about 85–90% by age 60, meaning that 85–90 out of 100 individuals inheriting a LFS gene alteration will develop one of the five characteristic cancers by the time he/she reaches 60 years of age. Much of this risk occurs in childhood through middle adulthood with the majority of individuals developing cancer by the time they reach 30 years of age.

Genetic profile

Li-Fraumeni syndrome follows autosomal dominant **inheritance** meaning that every individual diagnosed with LFS has a 50% (1 in 2) chance of passing on the condition to each of his/her children. Nearly every individual inheriting the LFS gene alteration will develop at least one of the characteristic tumors. However, not every family member inheriting the LFS gene alteration will develop the same kind of tumor. Additionally, some family members may develop more than one tumor whereas other family members may develop one tumor. For example, a family history may include a father who was diagnosed with a brain tumor at age 50, a daughter who was diagnosed with an adrenocortical carcinoma at age three and breast cancer at age 43 years, and a granddaughter who was diagnosed with sarcoma at age seven.

The majority of families with LFS have an alteration in a gene located on the short arm of chromosome 17 at location p53. There may be another gene(s) involved in LFS but as of 2001, no other gene has been identified in families in LFS.

KEY TERMS

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Mammography—X rays of the breasts; used to screen for breast cancer.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Primary tumor—The organ or tissue where the tumor began.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Stage—The extent of the tumor. Tests will be done to determine if the tumor is localized to the organ or if it has spread to the lymph nodes and/or other organs. Treatment depends upon the stage of the cancer.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

Demographics

Li-Fraumeni syndrome is a rare condition. About 300 families worldwide have been reported in the medical literature, however, not all families with LFS have been published in the medical literature. Males and females are equally affected.

Signs and symptoms

General symptoms of cancer include unexplained weight loss, weakness, fatigue, and pain. Symptoms specific to each characteristic tumor are listed below. It should be noted that the same kind of cancer may cause different symptoms in different people as well as that individuals with LFS may develop other kinds of cancer; consequently, any new and/or unusual symptom should be evaluated by a physician.

Adrenocortical carcinomas may cause abdominal pain. In some cases, the tumor causes extra hormones to be produced, and if so, the individual may experience high blood pressure, diabetes, deepening of the voice, swelling of the sexual organs and/or breasts or growth of hair on the face.

Brain cancer may result in a number of symptoms including vomiting, seizures, headaches, behavioral changes or problems, changes in eating or sleeping patterns, fatigue or clumsiness.

Breast cancer typically results in a lump. Occasionally, the nipple may invert or the skin over the lump may dimple. In rare cases, the breast may suddenly become red and swollen. Breast cancer can be identified before symptoms develop by the use of mammography.

Leukemia may result in unusual bruising, a pale appearance and/or recurrent infections. Little red or purple spots, called petechiae, may develop on the skin.

Sarcomas result in different symptoms depending upon the type of sarcoma. Osteosarcomas often lead to swelling and pain, symptoms that may be confused with an injury. Rhabdomyosarcomas cause a lump to develop and swelling.

Diagnosis

Evaluation of a family history for LFS requires a detailed three-generation family tree as well as medical records and/or death certificates to confirm or clarify the tissues involved as well as the age of the individual at the time of his/her diagnosis. Diagnosis of LFS depends upon the types of tumors family members have developed and the ages at which the tumors were diagnosed. A set of criteria for diagnosing LFS has been established.

A family may not meet the criteria for diagnosis of LFS but may have features that suggest LFS. Families such as these may be said to be "Li-Fraumeni-like" (LFL). Two sets of criteria have been developed for LFL, which like the diagnostic criteria, are based upon the high incidence of tumors in these families and the earlier ages of diagnosis.

Caution needs to be used when evaluating a family history of early-onset breast cancer, i.e. diagnosis in the twenties and thirties, since several other genes besides p53 are known to result in women having an increased risk for developing breast cancer at young ages. The clinical features of these other genes need to be taken into account and evaluated for while evaluating a family for LFS.

Genetic testing for p53 gene mutations is available and provides an additional method for making a diagnosis. It may be offered to an individual who has developed one of the tumors characteristic of LFS and who has a family history that meets the diagnostic criteria or strongly suggests LFS in order to confirm the diagnosis of LFS in the family. This is referred to as diagnostic testing. If a mutation is identified, the positive test result provides proof of the diagnosis. If no mutation is identified, this negative test result does not necessary remove the diagnosis of LFS. Genetic testing may not identify a

mutation for two reasons. First, laboratory techniques are not perfect and not every mutation in the p53 gene has been or can be identified; as of 2001, about 70 to 80% of mutations are identifiable. Second, there may be another gene(s) involved in LFS, but as of 2001, a second gene has not been identified and it is not known for certain whether there is second gene involved in LFS.

Genetic testing for LFS may be offered for a second reason. Genetic testing may be offered to an individual who has no personal history of cancer but whose family history meets the diagnostic criteria for LFS or is strongly suggestive of LFS. It is usually offered in order to determine this individual's risk for developing cancer and to help with decisions regarding medical screening. Genetic testing in this case is referred to as predictive or presymptomatic genetic testing. Predictive genetic testing should not be done unless a p53 genetic alteration has already been identified in an affected family member.

Genetic testing for diagnostic and predictive purposes is associated with significant risks and limitations, uncertain benefits and is best done with a geneticist (a doctor specializing in genetics) and/or genetic counselor knowledgeable about LFS and the implications of genetic testing. As of 2001, predictive genetic testing for LFS does not clearly provide a benefit for all family members at-risk for inheriting a familial p53 gene alteration since medical screening and prevention methods are not available for the tumors associated with LFS.

Prenatal diagnosis of LFS is available only if a p53 genetic alteration has already been identified in the family. Prenatal diagnosis of LFS is considered to be predictive genetic testing and therefore, the issues surrounding predictive genetic testing exist in this situation. An additional issue is how is the test result will be used with regard to continuation of the pregnancy. Individuals considering prenatal diagnosis of LFS should confirm its availability prior to conception.

Treatment and management

There is no cure or method for preventing LFS. Treatment depends upon the tumor(s) an individual develops. An individual does not require treatment until a tumor develops and then, the treatment will be specific to the type of tumor that has developed. An individual without symptoms, should, as indicated below, undergo regular medical check-ups.

In general, tumors are treated by surgery, chemotherapy and/or radiation therapy. Adrenocortical carcinomas and breast cancers, depending upon the stage of the tumor, use one or more of these treatments. Brain cancer is treated by surgery and/or radiation. In some cases, chemotherapy is also used. Leukemia is primarily treated by chemotherapy. In some cases, bone marrow transplantation is used. Osteosarcoma is treated by surgery. Rhabdomyosarcoma is treated by surgery, chemotherapy and radiation therapy.

TABLE 1

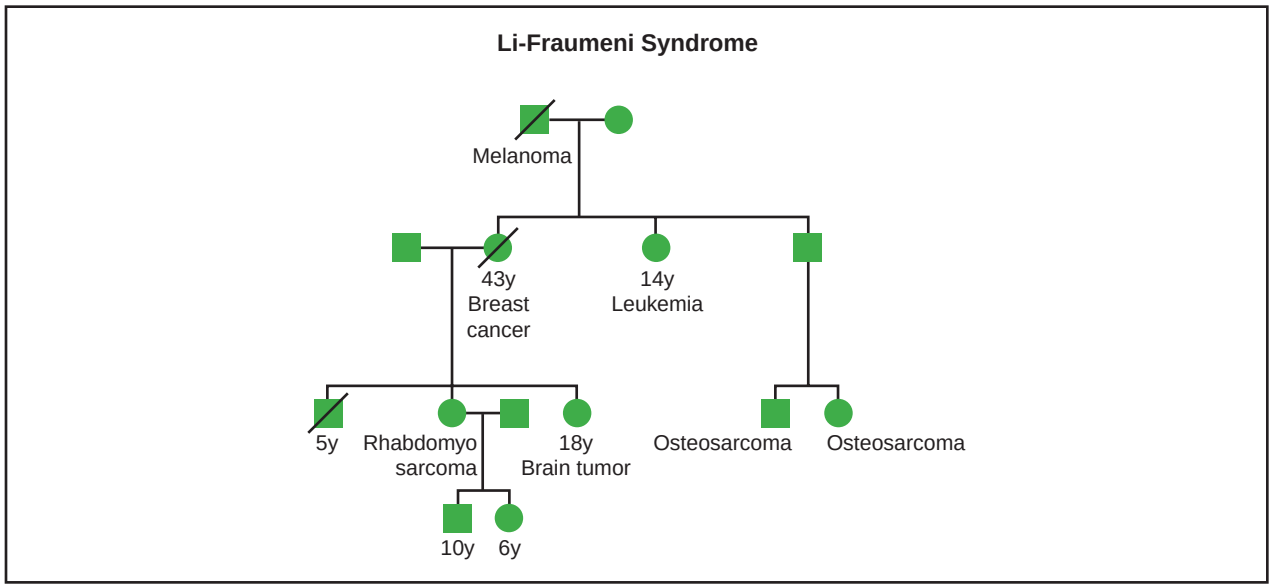
Age of onset for cancers associated with Li-Fraumeni syndrome

Age of onset	Type of cancer
Infancy	Development of adrenocortical carcinoma
Under 5 years of age	Development of soft-tissue sarcomas
Childhood and young adulthood	Acute leukemias and brain tumors
Adolescence	Osteosarcomas
Twenties to thirties	Premenopausal breast cancer is common

There are no proven methods of screening for or preventing cancer in individuals with LFS, other than perhaps breast cancer. It is very important that an individual's physician is aware of the family history and the cancer risk. It has been suggested that children of a parent with LFS be followed by having a complete physical examination, urinalysis, complete blood count (CBC) and abdominal ultrasound examination once each year. For adults at-risk for having inherited a familial p53 gene alteration, it has been suggested that they undergo a complete physical examination with skin, nervous system and rectal examinations once a year and that women undergo a clinical breast examination every six months and mammography once a year. As of 2001, there is controversy concerning the use of mammography in women with LFS because of some suggestion that p53 gene alterations are sensitive to radiation. In general, an individual may decrease his/her chance of developing cancer by not smoking, exercising on a regular basis, eating a healthy diet, limiting sun exposure and limiting his/her alcohol intake. Lastly, an individual with or at-risk for LFS should not delay seeing his/her physician if he/she notices a new or unusual symptom.

Prognosis

An individual who has LFS has a very high chance of developing a cancerous tumor by the time he/she is 60 years old. In contrast, individuals in the general population have about a 2% risk for developing cancer. The cancers associated with LFS each have a different prognosis and so, an individual's prognosis is highly dependent upon the type of cancer he/she has developed. In some cases, prognosis is associated with how early the cancer has been found. For example, breast cancer found early has a better prognosis than breast cancer found later. In general, the cancers typically seen in LFS are curable if caught early. For this reason, regular medical screening is



(Gale Group)

important. Prognosis may also be affected by the individual's overall health; consequently, being healthy and engaging in healthy behaviors may increase the chances of a good outcome.

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ORGANIZATIONS

National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda, MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

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Cindy L. Hunter, MS, CGC

Limb-girdle muscular dystrophy

Definition

Limb-girdle muscular dystrophy encompasses a diverse group of hereditary degenerative muscle disorders characterized by weakness and deterioration of the skeletal muscles.

Description

The term limb-girdle muscular dystrophy (LGMD) is used to describe a group of muscular dystrophies that

TABLE 1

Genetic causes of the limb-girdle muscular dystrophies

Type	Mode of Inheritance	Gene Involved	Chromosomal Location
*Alpha-sarcoglycanopathy	Recessive	LGMD2D (SGCA)	17
*Beta-sarcoglycanopathy	Recessive	LGMD2E (SGCB)	4
*Gamma-sarcoglycanopathy	Recessive	LGMD2C (SGCG)	13
*Delta-sarcoglycanopathy	Recessive	LGMD2F (SGCD)	5
Calpainopathy	Recessive	LGMD2A (CAPN3)	15
Dysferlinopathy	Recessive	LGMD2B (DYSF)	2
Telethoninopathy	Recessive	LGMD2G	17
LGMD2H	Recessive	LGMD2H	9
LGMD2I	Recessive	LGMD2I	19
LGMD1A	Dominant	LGMD1A	5
LGMD1B	Dominant	LGMD1B	1
Caveolinopathy	Dominant	LGMD1C (CAV3)	3
LGMD1D	Dominant	LGMDID	6
LGMD1E	Dominant		7
Bethlem myopathy	Dominant	COL6A1	21
	Dominant	COL6A2	21
	Dominant	COL6A3	2

*Each type of sarcoglycanopathy can result from a gene change that results in complete absence of sarcoglycan protein or decreased amounts of sarcoglycan protein.

cause a muscle deterioration that primarily affects the voluntary muscles around the limb girdle. The muscles of the limb girdle include those around the shoulders and hips. As the disease develops, the distal muscles of the limbs can be affected. In some cases the muscles of the heart can also be affected. There are at least 15 different LGMD that each have a different range of symptoms. Each of the muscular dystrophies result in an absent, deficient or abnormal protein that is required for normal structure and function of the muscles. It can be difficult to differentiate LGMD from other muscular dystrophies and muscle disorders which can also result in a weakness in the limb girdle.

Genetic profile

Each type of limb-girdle muscular dystrophy (LGMD) is caused by changes in a different type of **gene** that produces a protein normally involved in the functioning of the skeletal muscles (see table 1). Each gene is found at a specific location on a chromosome. We inherit two of each type of gene, one from our mother and one from our father. Each type of gene produces a specific type of protein. A change (mutation) in a gene can cause it to produce abnormal protein, an increased or decreased amount of normal protein or can cause it to stop producing protein altogether. Abnormal or decreased amounts of skeletal muscle proteins can affect the development or functioning of the muscle cells, causing the symptoms of LGMD. Most forms of LGMD are autosomal recessive although some rare forms are autosomal dominant.

An autosomal recessive form of LGMD is caused by a change in both genes of a pair. One of the changed genes is inherited from the egg cell of the mother and one of the changed genes is inherited from the sperm cell of the father. Parents who have a child with an autosomal recessive form of LGMD are called carriers, since they each possess one changed LGMD gene and one unchanged LGMD gene. Carriers do not have any symptoms since they have one unchanged gene, which produces enough normal protein to prevent the symptoms of LGMD. Each child born to parents who are both carriers for the same type of LGMD, has a 25% chance of having LGMD, a 50% chance of being a carrier and a 25% chance of being neither a carrier nor affected with LGMD. Parents who are carriers for different types of LGMD are not at increased risk for having affected children.

The autosomal dominant forms of LGMD are caused by a change in only one gene of a pair. Sometimes this changed gene is inherited from either the mother or the father. If the changed gene is inherited, then each sibling of the person with LGMD has a 50% chance of inheriting the condition. Sometimes the change occurs spontaneously when the egg and sperm come together to form the first cell of the baby. In this case other relatives, such as siblings, are not at increased risk for inheriting LGMD. A person with an autosomal dominant form of LGMD has a 50% chance of passing the condition on to his or her

TABLE 2

Frequency of limb–girdle muscular dystrophies

Type	Frequency	Most Common In:
Alpha-sarcoglycanopathy		None
Beta-sarcoglycanopathy	Majority with severe disease—	Amish
Gamma-sarcoglycanopathy	10% of those with mild disease	North Africans; Gypsies
Delta-sarcoglycanopathy		Brazilian
Calpainopathy	Approximately 10%—30%	Amish; La Reunion Isle.; Basque (Spain); Turkish
Dysferlinopathy	Approximately 10%	Libyan Jews
Telethoninopathy	Rare	Italian
LGMD2H	Unknown	Unknown
LGMD2I	Unknown	Unknown
LGMD1A	Rare	Unknown
LGMD1B	Rare	Unknown
Caveolinopathy	Rare	Unknown
LGMD1D	Rare	Unknown
LGMD1E	Rare	Unknown
Bethlem myopathy	Rare	Unknown

children. Some people who posses an autosomal dominant LGMD gene change do not have any symptoms.

Demographics

The incidence of LGMD is not known since it can have a wide range of symptoms and is difficult to differentiate from other muscular disorders. Some forms of LGMD are found more commonly in people of a certain ethnic background (see table 2). LGMD is found equally in men and women.

Signs and symptoms

Each type of LGMD has a different range of symptoms (see table 3). The symptoms can even vary between individuals with the same type of LGMD. The age of onset of symptoms varies tremendously and can range from infancy to adulthood. The most common symptom of LGMD is muscle weakness and deterioration involving the muscles around the hips and shoulders. The disorder progresses at a different rate in different people. The progression and extent of muscle deterioration cannot be predicted, although individuals with an onset of the disorder in adulthood may have a slower progression and milder symptoms.

The first noticeable symptom of LGMD is often a "waddling" gait due to weakness of the hip and leg muscles. Difficulties in rising from a chair or toilet seat and difficulties in climbing stairs are common. Eventually walking may become so difficult that a wheelchair or scooter is necessary for locomotion. Enlargement or a decrease in size of the calf muscles can also be seen. Contractures and muscle cramps are experienced by some individuals with LGMD. The limited mobility associated with LGMD can result in muscle soreness and joint pain.

Lifting heavy objects, holding the arms outstretched and reaching over the head can become difficult because of weaknesses in the shoulder muscles. Some individuals with LGMD may even eventually have difficulties swallowing and feeding themselves. Sometimes the back muscles can become weakened and result in **scoliosis** (curvature of the spine).

LGMD can occasionally result in a weakening of the heart muscles and/or the respiratory muscles. Some people may experience a weakening of the heart muscles called a cardiomyopathy. Others may develop a conduction defect, an abnormality in the electrical system of the heart that regulates the heartbeat. A weakening of the muscles necessary for respiration can cause breathing difficulties. LGMD does not affect the brain and the ability to reason and think. Individuals with LGMD also maintain normal bladder and bowel control and sexual functioning.

Diagnosis

There is no single test available to diagnose LGMD. A diagnosis is based on clinical symptoms, physical examinations, and a variety of tests. The doctor will often first take a medical history to establish the type of symptoms experienced and the pattern of muscle weakness. He or she will usually ask questions about the family history to see whether other family members have similar symptoms.

It is necessary for the doctor to establish whether the weakness is due to problems with the muscles or due to

TABLE 3

Symptoms of the limb-girdle muscular dystrophies

Type	Age of Onset	Early Symptoms	Late Symptoms
*Sarcoglycanopathy (complete deficiency)	3–15 years (8.5 average)	Proximal weakness Difficulty walk/run Enlarged calf muscles	Contractures Curvature in the spine Wheelchair bound Possible cardiac conduction defect Dilated cardiomyopathy
**Sarcoglycanopathy (partial deficiency	Adolescence/Young adulthood	Muscle cramp	
Calpainopathy	2–40 years (8–15 average)	Intolerance to exercise Proximal weakness Jutting backwards of shoulder blades (scapular winging) Decreased size of calf muscles Contractures Curvature in the spine	Wheelchair bound
Dysferlinopathy	17–23 years	Some patients have distal weakness and some have proximal weakness Inability to tip-toe Difficulties walk/run	
Telethoninopathy	Early teens		Wheelchair bound
LGMD2H	8–27 years		Wheelchair bound
LGMD2I	1.5–27 years		Wheelchair bound
LGMD1A	18–35 years	Proximal leg and arm weakness Tight Achilles tendon Problems with articulation of speech Nasal sounding speech	Distal weakness
LGMD1B	4–38 years (50% onset childhood)	Proximal lower limb weakness	Contractures Irregular heart beat Sudden death due to cardiac problems (if untreated)
LGMD1D	<25 years	Proximal muscle weakness Cardiac conduction defect Dilated cardiomyopathy	All patients remain able to walk
LGMD1E	9–49 years (30 average)	Proximal lower and upper limb muscle weakness	Contractures Difficulties swallowing
Caveolinopathy	Approx. 5 years	Mild to moderate proximal weakness Muscle cramping Enlargement of the calf muscles Some have no symptoms	
Bethlem myopathy	<2 years	Floppy muscles in infancy Proximal muscle weakness Contractures	2/3 of patents are wheelchair bound by age 50

* Includes alpha, beta, gamma and delta sarcoglycanopathies that result in complete absence of a sarcoglycan protein

**Includes alpha, beta, gamma and delta sarcoglycanopathies that result in decreased amounts of a sarcoglycan protein

a problem with the nerves that control the muscles. Sometimes this can be accomplished through a physical examination. Testing called electromyography is often performed to establish whether the weakness is nerve or muscle based. During electromyography a needle electrode is inserted into the muscle. Electromyography measures the electrical activity of the muscle in response to stimulation by the nerves.

A blood test that measures the amount of creatine kinase is often performed. Creatine kinase is an enzyme that is produced by damaged muscle. High levels of creatine kinase suggest that the muscle is being destroyed, but do not indicate the cause of the damage. The most common causes of increased creatine kinase are muscular dystrophy and an inflammation of the muscle.

A muscle biopsy will often be performed if LGMD is suspected. During the muscle biopsy, a small amount of muscle is surgically removed. The muscle sample is examined under the microscope to check for changes that are characteristic of muscular dystrophies. The amount and type of muscle proteins present in the sample of muscle can sometimes help to confirm a diagnosis of LGMD and can sometimes indicate the type of LGMD.

A diagnosis can be difficult to make since there are many types of LGMD and a wide range of symptoms. It can also be difficult to differentiate LGMD from other muscular dystrophies that have similar symptoms such as Becker and **Duchenne muscular dystrophy**. Anyone suspected of having LGMD should, therefore, consider undergoing testing for other types of muscular dystrophies.

As of 2001, DNA testing for the different forms of LGMD is not available through clinical laboratories.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic sac—Contains the fetus which is surrounded by amniotic fluid.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Cardiac conduction defect—Abnormality of the electrical system of the heart which regulates the heart beat.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Dilated cardiomyopathy—A diseased and weakened heart muscle that is unable to pump blood efficiently.

Distal muscles—Muscles that are furthest away from the center of the body.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Limb girdles—Areas around the shoulders and hips.

Prenatal testing—Testing for a disease, such as a genetic condition, in an unborn baby.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Proximal muscles—The muscles closest to the center of the body.

Scapular winging—The jutting back of the shoulder blades that can be caused by muscle weakness.

Skeletal muscle—Muscles under voluntary control that attach to bone and control movement.

DNA testing is difficult since there are many genes and types of gene changes that can cause LGMD. Some research laboratories are looking for the gene changes that cause LGMD and may detect the gene change or changes responsible for LGMD in a particular individual. DNA testing may be performed on a sample of blood cells or a sample of muscle cells. If an autosomal dominant gene change is detected in someone with LGMD then both of his or her parents can be tested to see if the gene change was inherited. If the gene change was inherited then siblings can be tested to see if they have inherited the changed gene. If autosomal recessive gene changes are detected then relatives such as siblings can be tested to see if they are carriers.

Prenatal testing for LGMD is only available if DNA testing has detected an autosomal dominant LGMD gene change in one parent or an autosomal recessive gene change in both parents. Cells for prenatal testing are obtained through an **amniocentesis** or chorionic villus sampling. These cells are analyzed for the LGMD gene change or changes that were found in one or both parents.

Treatment and management

Physical therapy and exercises can often help keep the muscles and joints mobile and prevent contractures. Muscle and joint pain can be treated through exercise, warm baths and pain medications. Surgical treatment of complications such as a curved spine may be necessary. Breathing exercises can sometimes help if breathing becomes difficult. If breathing independently becomes impossible then a portable mechanical ventilator can be

used. A wheelchair or scooter can help when walking becomes difficult. Medications are often prescribed for cardiomyopathies and heart conduction defects. A device such as a pacemaker that creates normal contractions of the heart muscle may be necessary for some people with heart muscle abnormalities.

Gene therapy may one day cure LGMD. Gene therapy introduces unchanged copies of a LGMD gene into the muscle cells. The goal of therapy is for the normal LGMD gene to produce normal protein that will allow the muscle cells to function normally. As of 2001 gene therapy clinical trials have been temporarily halted but they are likely to continue in the near future. It will take quite a few years, however, for gene therapy to become a viable way to treat LGMD.

Prognosis

The prognosis of LGMD varies tremendously. Most people with LGMD, however do not have severe symptoms and most experience a normal lifespan. Cardiac and respiratory difficulties can, however, decrease the lifespan.

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ORGANIZATIONS

Muscular Dystrophy Association—Canada. 2345 Yonge St., Suite 900, Toronto, ONT M4P 2E5. Canada (416) 488-2699. info@mdac.ca. <http://www.mdac.ca/main.html>.

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

Muscular Dystrophy Campaign. 7-11 Prescott Place, London, SW4 6BS. UK +44(0) 7720 8055. info@muscular-dystrophy.org. <http://www.muscular-dystrophy.org>.

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Lisa Maria Andres, MS, CGC

Lipoprotien-lipase deficency *see* **Hyperlipoproteinemia Type I**

Lissencephaly

Definition

Lissencephaly, literally meaning smooth brain, is a rare birth abnormality of the brain that results in profound mental retardation and severe seizures.

Lissencephaly is caused by an arrest in development of the fetal brain during early pregnancy. The cerebral cortex, the top layer of the brain controlling higher thought processes, does not develop the normal sulci, the indentations or valleys in the cortex, and gyri, the ridges or convolutions seen on the surface of the cortex. Instead, the cortex in a person with lissencephaly is thickened and smooth with disorganized neurons that have not migrated to their proper places. The typical cortex has six layers of neurons, but brains with lissencephaly usually have only four.

Description

The condition was first reported in 1914 by pathologists Culp and Erhardt, who described a human brain with a smooth surface, lacking the normal gyri. They called it lissencephaly.

Lissencephaly is one of a number of conditions called "neural migration disorders" that occur because the developing neurons do not proceed correctly to their normal place in the brain's cortex during fetal development. In fact, the brain of a person with lissencephaly, with its smooth and immature cortex, resembles a typical human fetal brain at about 10 to 14 weeks of development.

Children with lissencephaly are almost always severely to profoundly mentally retarded, and the vast majority develop seizures that are difficult to treat. Life expectancy is reduced, and survivors need constant care.

Lissencephaly can occur as an isolated birth abnormality or can be one of many birth abnormalities occurring together in a specific inherited syndrome. There are at least 10 inherited syndromes that include lissencephaly and many more that include variants of this brain malformation. Lissencephaly can also occur by itself without other characteristics.

Some cases of lissencephaly are caused by new changes in the genetic material of that particular baby—these cases are caused by sporadic, or random, gene

KEY TERMS

Agyria—The absence of gyri, or convolutions, in the cerebral cortex.

Cerebellum—A portion of the brain consisting of two cerebellar hemispheres connected by a narrow vermis. The cerebellum is involved in control of skeletal muscles and plays an important role in the coordination of voluntary muscle movement. It interrelates with other areas of the brain to facilitate a variety of movements, including maintaining proper posture and balance, walking, running, and fine motor skills, such as writing, dressing, and eating.

Cerebral cortex—The outer surface of the cerebrum made up of gray matter and involved in higher thought processes.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Heterotopia—Small nodules of gray matter that are present outside the cortex.

Lissencephaly—A condition in which the brain has a smooth appearance because the normal convolutions (gyri) failed to develop.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Microcephaly—An abnormally small head.

Pachygyria—The presence of a few broad gyri (folds) and shallow sulci (grooves) in the cerebral cortex.

Prenatal diagnosis—The determination of whether a fetus possesses a disease or disorder while it is still in the womb.

Subcortical band heterotopia—A mild form of lissencephaly type 1 in which abnormal bands of gray and white matter are present beneath the cortex near the ventricles.

Ventricle—The fluid filled spaces in the center of the brain that hold cerebral spinal fluid.

mutations (also called *de novo*). This means that the genetic change is not present in the parents or anyone else in the family. Some cases of lissencephaly are caused by rearrangements of chromosome material that can be inherited from a healthy parent. Other types of lissencephaly are inherited in an autosomal recessive pattern. This means that a couple who has a child with an autosomal recessive lissencephaly syndrome has a 25% chance in any future pregnancy to have another affected child. There are also types of lissencephaly caused by changes in a gene or genes on the X chromosome. X-linked lissencephaly affects mainly males, who have only one X chromosome. Females who carry an X-linked gene change on one of their two X **chromosomes** often have mild brain changes.

Other known causes of lissencephaly include viral infections of the fetus or insufficient blood supply to the brain during the first trimester of pregnancy.

Genetic profile

There are a number of subtypes of lissencephaly that are distinguished by differences in the physical structure of the brain. “Classical,” or type 1, lissencephaly and cobblestone **dysplasia**, or type 2, lissencephaly are the most common subtypes.

Classical, or type 1, lissencephaly consists of a brain surface that is completely smooth except for a few shallow valleys (sulci). The cortex is thicker than normal and there are clumps of neurons found in areas outside the cortex (heterotopia). The corpus callosum, the band of tissue between the hemispheres of the brain, is often small and is sometimes absent. The posterior ventricles, the fluid-filled spaces in the center of the brain, are often larger than normal.

Type 1 lissencephaly can be seen in a number of genetic syndromes and can also occur by itself in a condition called Isolated Lissencephaly Sequence (ILS). The vast majority of cases of ILS is a result of mutations or deletions (missing sections) in one of two different genes involved in brain development.

The gene causing the majority of cases of ILS is called the LIS1 and is located on the short arm of chromosome 17. Between 40% and 64% of persons with ILS have a deletion of a portion of the LIS1 gene, and about 24% have a mutation that disrupts the normal function of the gene. Most deletions and mutations in the LIS1 gene are sporadic and are not present in other family members.

Another 12% of persons with ILS have a mutation in a gene called XLIS (or DCX), located on the long arm of the X chromosome. Mutations in XLIS cause X-linked lissencephaly in males and may or may not cause symptoms in the mothers who carry the mutation.

There are also a few cases of ILS that appear to be inherited in an autosomal recessive pattern. As of 2001, the mutated genes for this and other types of ILS have not been discovered.

TABLE 1

Associated forms of Lissencephaly

Disorder	Inheritance	Gene location	Proportion of patients	Gene name	Protein product	Clinical test
MDS (Miller-Dieker syndrome)	AD	17p13.3	100%	LIS1	Platelet activating factor Acetylhydrolase 45K	Yes
ILS1 (Isolated lissencephaly sequence 1)	AD	17p13.3	>40%	LIS1	Platelet activating factor acetylhydrolase 45K	Yes
X-linked lissencephaly and subcortical band heterotropia	X-linked	Xq22.3–q23	Unknown	XLIS	Unknown	No
Cobblestone lissencephaly (lissencephaly type 2)	AR	Unknown	Unknown	Unknown	Unknown	No

An example of a genetic syndrome involving type 1 lissencephaly is Miller-Dieker syndrome (MDS). This disorder is caused by a deletion of part of the short arm of chromosome 17 (17p13) that includes the LIS1 gene. In addition to lissencephaly, children with MDS have distinctive facial features including a high forehead, short upturned nose, and thin lips. They also have narrowing at the temples and a small jaw, although these traits can also be seen in ILS and other lissencephaly syndromes. Children with MDS occasionally have other birth abnormalities of the heart, kidneys, or palate. Calcium deposits in the midline of the brain are common in MDS, but not in ILS or other syndromes.

Type 2 lissencephaly is also called cobblestone dysplasia because of the pebbled appearance to the surface of the cerebral cortex. Brains with cobblestone dysplasia often show abnormalities of the white matter, enlarged ventricles, underdeveloped brainstem and cerebellum, and absence of the corpus callosum. There are four known syndromes that include cobblestone dysplasia: cobblestone lissencephaly without other birth defects (CLO); Fukuyama congenital **muscular dystrophy** (FCMD); muscle-eye-brain disease (MEB); and **Walker-Warburg syndrome** (WWS). These disorders are quite rare and all are inherited in an autosomal recessive pattern. Diagnosis depends on MRI studies and clinical evaluations. As of 2001, there are no specific genetic tests available for clinical use for these conditions.

There are other rare syndromes involving lissencephaly and variants of lissencephaly, some of which are autosomal recessive and some X-linked. None of the genes responsible for these other conditions have been identified as of Spring 2001.

Demographics

Lissencephaly affects fewer than one in 100,000 individuals and occurs in all parts of the world. The sporadic and autosomal recessive types of lissencephaly occur equally in males and females. X-linked syndromes that include lissencephaly occur mainly in boys, although carrier mothers sometimes have milder signs.

Signs and symptoms

Many babies with lissencephaly appear normal at birth, although some have immediate respiratory problems. After the first few months at home, parents typically notice feeding problems, inability to visually track objects, and lessened activity in their child. Breath-holding spells (apnea) and muscle weakness are also common. Seizures frequently begin within the first year of life, are usually severe, and are difficult to treat with medication. Muscle weakness changes to spasticity (a condition of excessive muscle tension) over time. Repeated pneumonias from swallowing food down the airway and into the lungs are common.

Head size is usually within normal limits at birth; however, as the baby's body grows, head growth lags and a small head (microcephaly) results. Babies with isolated lissencephaly often have hollowing at the temples and small jaws, both thought to be a result of the abnormal brain shape. Genetic syndromes involving lissencephaly will include other symptoms and signs.

Diagnosis

The diagnosis of lissencephaly is initially based on tests using magnetic resonance imaging (MRI) and CT testing. MRI findings in type 1 lissencephaly include a lack of, or very shallow, convolutions on the surface of an unusually thick cerebral cortex. Enlargement of the ventricles is sometimes present.

On average, persons with Miller-Dieker syndrome have more severe MRI findings than persons with ILS. It is sometimes possible to distinguish between chromosome 17-related lissencephaly (ILS and MDS) and X-linked ILS based on MRI findings. The smooth brain appearance is more striking in the back portion of the brain in persons with chromosome 17 LIS1 deletions and mutations. In contrast, it is more conspicuous in the front part of the brain in persons with XLIS mutations. In addition, underdevelopment of part of the cerebellum is more commonly seen in persons with XLIS mutations.

Individuals with subcortical band heterotopia (SBH), a milder form of lissencephaly often seen in female carriers of XLIS, often have minor changes in the gyri, shallow sulci, and ribbons of white and gray matter beneath the cortex that show up on MRIs.

MRI findings in type 2 lissencephaly can include a cobblestone appearance of the cortex, enlarged ventricles, abnormalities of the white matter, and changes in the cerebellum, corpus callosum and brain stem.

A CT scan can be done to look for calcium deposits in the midline of the brain. Calcium deposits are common in MDS but not found in other lissencephaly syndromes.

In addition to MRI and CT testing, a careful clinical evaluation and examination by a medical geneticist is necessary to confirm the diagnosis and evaluate the child for the presence of a syndrome. It is essential for a child to have a precise diagnosis in order for genetic counselors to be able to give the family complete and accurate information about the **inheritance** pattern and chances for the condition to recur in future children.

To confirm the diagnosis of MDS or ILS, chromosome testing and other specialized genetic tests are often helpful. A test called fluorescence in situ hybridization (FISH) is used to detect LIS1 gene deletions. High resolution chromosome testing can often determine whether a deletion is sporadic or due to an inherited chromosome rearrangement. If necessary, mutation analysis, looking for specific errors in the sequence of the LIS1 or XLIS gene, can be performed.

Parents of a child with ILS who has a confirmed deletion or mutation in LIS1, and who have normal genetic studies themselves, have a less than 1% chance of having another child with ILS. Similarly, MDS with a confirmed sporadic deletion in LIS1 has a low chance of recurring. MDS caused by a chromosome rearrangement carries a higher chance of happening again. Actual risks depend on the specific rearrangement.

XLIS mutations are often inherited from a carrier mother. If a woman has **genetic testing** and is confirmed to have an XLIS mutation, she will have a 25% chance with each pregnancy to have an affected male and a 25% chance to have a carrier female who may have SBH.

If a detectable mutation, deletion, or chromosome rearrangement has been confirmed in the affected family member, prenatal diagnosis is available during future pregnancies. Ultrasound of the fetal anatomy during pregnancy cannot diagnose lissencephaly. However, ultrasound performed by a specialist at 18 to 22 weeks of pregnancy can sometimes detect other birth abnormalities that occur in some of the syndromes involving lissencephaly.

Treatment and management

There is no treatment or cure for lissencephaly. Seizures occur in almost all children with lissencephaly and are often difficult to control, even with the strongest anti-seizure medications. A severe type of seizure called infantile spasms can occur and may need to be treated with injections of adrenocorticotropic hormone (ACTH), although this treatment is not always effective.

Feeding difficulties can include choking, gagging, or regurgitating food or liquid. Aspiration, swallowing food down the trachea and into the lungs, is a serious problem that can lead to pneumonia. Liquids and thin foods can be thickened to make swallowing easier. There are medications available to help with reflux. Children who continue to have serious problems may need a permanent feeding tube placed into the stomach to ensure adequate nutrition.

Physical and occupational therapy can help prevent or reduce tightening of the joints and help to normalize muscle tone. However, the improvements are often limited and temporary.

Prognosis

Persons with classical lissencephaly usually need lifelong care for all basic needs. Many babies will not live past infancy, but the average age of survival depends on the particular syndrome involved, the type of lissencephaly, and the severity of the brain abnormalities in a given child. Babies with MDS usually die by two years of age, but the majority of persons with ILS live into childhood, although often not into adulthood. Many babies with cobblestone dysplasia die in infancy; however, some affected people have lived into their 20s. In contrast, persons with SBH have very variable signs and symptoms, may be asymptomatic, mildly affected or severely retarded, and may have near-normal or normal lifespans.

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American Epilepsy Society. 342 North Main St., West Hartford, CT 06117. (860) 586-7505. Fax: (860 586-7550. info@aesnet.org. <http://www.aesnet.org>.

Epilepsy Foundation of America. 4351 Garden City Dr., Suite 406, Landover, MD 20785-2267. (301) 459-3700 or (800) 332-1000. <http://www.epilepsyfoundation.org>.

Lissencephaly Network, Inc. 716 Autumn Ridge Lane, Fort Wayne, IN 46804-6402. (219) 432-4310. Fax: (219) 432-4310. lissennet@lissencephaly.org. <http://www.lissencephaly.org>.

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Barbara J. Pettersen

Liver cancer

Definition

Liver cancer is a form of cancer with a high mortality rate. Liver cancers can be classified into two types. They are either primary, when the cancer starts in the liver itself; or metastatic, when the cancer has spread to the liver from some other part of the body.

Description

Primary liver cancer

Primary liver cancer is a relatively rare disease in the United States, representing about 2% of all malignancies. It is, however, much more common in other parts of the world, representing from 10–50% of malignancies in Africa and parts of Asia. The American Cancer Society estimates that in the United States in 2001, at least 16,200 new cases of liver cancer will be diagnosed (10,700 in men and 5,500 in women), causing roughly 14,100 deaths.

In adults, most primary liver cancers belong to one of two types: hepatomas, or hepatocellular carcinomas, which start in the liver tissue itself; and cholangiomas, or cholangiocarcinomas, which are cancers that develop in the bile ducts inside the liver. About 75% of primary liver cancers are hepatomas. In the United States, about five persons in every 200,000 will develop a hepatoma; in Africa and Asia, over 40 persons in 200,000 will develop this form of cancer. Two rare types of primary liver cancer are mixed-cell tumors, or undifferentiated tumors.

There is one type of primary liver cancer that usually occurs in children younger than four years of age and between the ages of 12–15. This type of childhood liver cancer is called a hepatoblastoma. Unlike liver cancers in adults, hepatoblastomas have a good chance of being treated successfully. Approximately 70% of children with hepatoblastomas experience complete cures. If the tumor is detected early, the survival rate is over 90%.

Metastatic liver cancer

The second major category of liver cancer, metastatic liver cancer, is about 20 times as common in the United States as primary liver cancer. Because blood from all parts of the body must pass through the liver for filtration, cancer cells from other organs and tissues easily reach the liver, where they can lodge and grow into secondary tumors. Primary cancers in the colon, stomach, pancreas, rectum, esophagus, breast, lung, or skin are the most likely to spread (metastasize) to the liver. It is not unusual for the metastatic cancer in the liver to be the first noticeable sign of a cancer that started in another organ. After cirrhosis, metastatic liver cancer is the most common cause of fatal liver disease.

Genetic profile

Hepatocellular carcinoma has occasionally been reported to occur in familial clusters. It appears that first-degree relatives (siblings, children, or parents) of people with primary liver cancer are 2.4 times more likely to develop liver cancer themselves. This finding indicates a small overall genetic component, however, specific disease genes have not yet been identified. Certain genetic diseases are associated with a higher risk for liver cancers. These include **Hemochromatosis**, **alpha-1 Antitrypsin deficiency**, glycogen storage disease, tyrosinemia, **Fanconi anemia**, and **Wilson disease**.

Demographics

Hepatocellular carcinoma is the sixth most common cancer of men and eleventh most common cancer of women worldwide, affecting 250,000 to one million individuals annually. Liver cancer is becoming more common in the United States. It is 10 times more common in

KEY TERMS

Aflatoxin—A substance produced by molds that grow on rice and peanuts. Exposure to aflatoxin is thought to explain the high rates of primary liver cancer in Africa and parts of Asia.

Alpha-fetoprotein (AFP)—A chemical substance produced by the fetus and found in the fetal circulation. AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

Cirrhosis—A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

Hepatitis—A viral disease characterized by inflammation of the liver cells (hepatocytes). People infected with hepatitis B or hepatitis C virus are at an increased risk for developing liver cancer.

Metastatic cancer—A cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.

Africa and Asia where liver cancer is the most common type of cancer. Liver cancer affects men more often than women and, like most cancers, it is more common in older individuals.

Risk factors for primary liver cancer

The exact cause of primary liver cancer is still unknown. In adults, however, certain factors are known to place some individuals at higher risk of developing liver cancer. These factors include:

- Exposure to hepatitis B (HBV) or hepatitis C (HBC) viruses. In Africa and most of Asia, exposure to hepatitis B is an important factor; in Japan and some Western countries, exposure to hepatitis C is connected with a higher risk of developing liver cancer. In the United States, nearly 25% of patients with liver cancer show evidence of HBV infection. Hepatitis is commonly found among intravenous drug abusers.
- Exposure to substances in the environment that tend to cause cancer (carcinogens). These include a substance produced by a mold that grows on rice and peanuts (aflatoxin); thorium dioxide, which was used at one time as a contrast dye for x rays of the liver; and vinyl chloride, a now strictly regulated chemical used in manufacturing plastics.
- Cirrhosis. Hepatomas appear to be a frequent complication of cirrhosis of the liver. Between 30 and 70% of hepatoma patients also have cirrhosis. It is estimated that a patient with cirrhosis has 40 times the chance of developing a hepatoma than a person with a healthy liver.
- Use of oral estrogens for birth control. This association is based on studies of older, stronger birth control pills that are no longer prescribed. It is not clear if newer, lower dose birth control pills increase risk for liver cancer.
- Use of anabolic steroids (male hormones) for medical reasons or strength enhancement. Cortisone-like steroids do not appear to increase risk for liver cancer.
- Hereditary hemochromatosis. Hemochromatosis is a disorder characterized by abnormally high levels of iron storage in the body. It often develops into cirrhosis.
- Geographic location. Liver cancer is 10 times more common in Asia and Africa than in the United States.
- Male sex. The male/female ratio for hepatoma is 4:1.
- Age over 60 years.

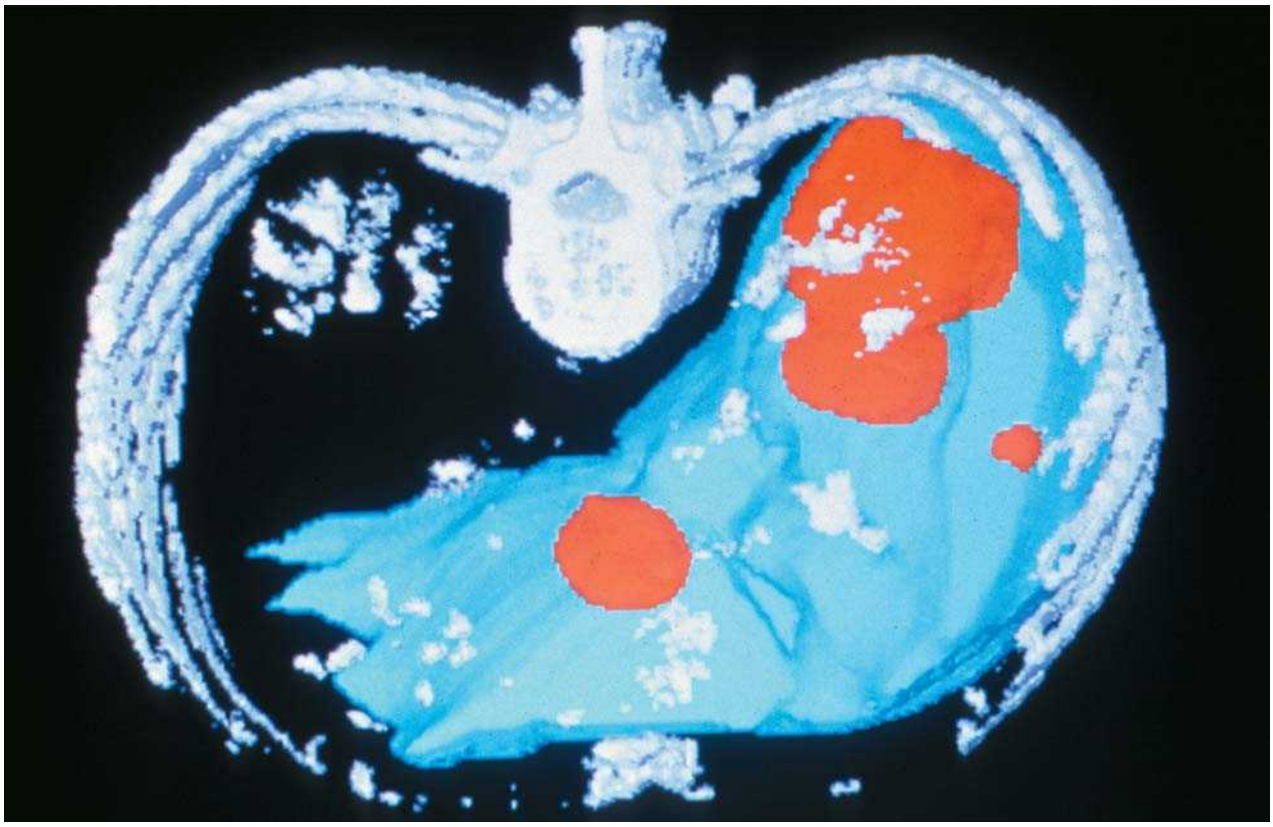
Signs and symptoms

The early symptoms of primary, as well as metastatic, liver cancer are often vague and not unique to liver disorders. The long lag time between the beginning of the tumor's growth and signs of illness is the major reason why the disease has such a high mortality rate. At the time of diagnosis, patients are often tired, with fever, abdominal pain, and loss of appetite. They may look emaciated and generally ill. As the tumor grows bigger, it stretches the membrane surrounding the liver (the capsule), causing pain in the upper abdomen on the right side. The pain may extend into the back and shoulder. Some patients develop a collection of fluid, known as ascites, in the abdominal cavity. Others may show signs of bleeding into the digestive tract. In addition, the tumor may block the ducts of the liver or the gall bladder, leading to jaundice. In patients with jaundice, the whites of the eyes and the skin may turn yellow, and the urine becomes dark-colored.

Diagnosis

Physical examination

If the doctor suspects a diagnosis of liver cancer, he or she will check the patient's history for risk factors and pay close attention to the condition of the patient's abdomen during the physical examination. Masses or lumps in the liver and ascites can often be felt while the



This 3-D CT (computed tomography) scan shows the abdomen of a patient with liver cancer. The metastatic tumors are red and located in the liver (blue). *(Photo Researchers, Inc.)*

patient is lying flat on the examination table. The liver is usually swollen and hard in patients with liver cancer; it may be sore when the doctor presses on it. In some cases, the patient's spleen is also enlarged. The doctor may be able to hear an abnormal sound (bruit) or rubbing noise (friction rub) if he or she uses a stethoscope to listen to the blood vessels that lie near the liver. The noises are caused by the pressure of the tumor on the blood vessels.

Laboratory tests

Blood tests may be used to test liver function or to evaluate risk factors in the patient's history. Between 50% and 75% of primary liver cancer patients have abnormally high blood serum levels of a particular protein (alpha-fetoprotein or AFP). The AFP test, however, cannot be used by itself to confirm a diagnosis of liver cancer, because cirrhosis or chronic hepatitis can also produce high alpha-fetoprotein levels. Tests for alkaline phosphatase, bilirubin, lactic dehydrogenase, and other chemicals indicate that the liver is not functioning normally. About 75% of patients with liver cancer show evidence of hepatitis infection. Again, however, abnormal liver function test results are not specific for liver cancer.

Imaging studies

Imaging studies are useful in locating specific areas of abnormal tissue in the liver. Liver tumors as small as an inch across can now be detected by ultrasound or computed tomography scan (CT scan). Imaging studies, however, cannot tell the difference between a hepatoma and other abnormal masses or lumps of tissue (nodules) in the liver. A sample of liver tissue for biopsy is needed to make the definitive diagnosis of a primary liver cancer. CT or ultrasound can be used to guide the doctor in selecting the best location for obtaining the biopsy sample. Chest x rays may be used to see whether the liver tumor is primary or has metastasized from a primary tumor in the lungs.

Liver biopsy

Liver biopsy is considered to provide the definite diagnosis of liver cancer. In about 70% of cases, the biopsy is positive for cancer. In most cases, there is little risk to the patient from the biopsy procedure. In about 0.4% of cases, however, the patient develops a fatal hemorrhage from the biopsy because some tumors are supplied with a large number of blood vessels and bleed very easily.

Laparoscopy

The doctor may also perform a laparoscopy to help in the diagnosis of liver cancer. A laparoscope is a small tube-shaped instrument with a light at one end. The doctor makes a small cut in the patient's abdomen and inserts the laparoscope. A small piece of liver tissue is removed and examined under a microscope for the presence of cancer cells.

Treatment

Treatment of liver cancer is based on several factors, including the type of cancer (primary or metastatic); stage (early or advanced); the location of other primary cancers or metastases in the patient's body; the patient's age; and other coexisting diseases, including cirrhosis. Treatment options include surgery, radiation, and chemotherapy. At times, two or all three of these may be used together. For many patients, treatment of liver cancer is primarily intended to relieve the pain caused by the cancer but cannot cure it.

Surgery

The goal of surgery is to remove the entire tumor, curing liver cancer. However, few liver cancers in adults can be cured by surgery because they are usually too advanced by the time they are discovered. If the cancer is contained within one lobe of the liver, and if the patient does not have cirrhosis, jaundice, or ascites, surgery is the best treatment option. Patients who can have their entire tumor removed have the best chance for survival.

If the entire visible tumor can be removed, about 25% of patients will be cured. The operation that is performed is called a partial hepatectomy, or partial removal of the liver. The surgeon will remove either an entire lobe of the liver (a lobectomy) or cut out the area around the tumor (a wedge resection).

Doctors may also offer tumor embolization or ablation. Embolization involves killing a tumor by blocking its blood supply. Ablation is a method of destroying a tumor without removing it. One method of ablation, cryosurgery, involves freezing the tumor, thereby destroying it. In another method of ablation, ethanol ablation, doctors kill the tumor by injecting alcohol into it. As of 2001, a new method of ablation using high-energy radio waves is under development.

Chemotherapy

Chemotherapy involves using very strong drugs, taken by mouth or intravenously, to suppress or kill tumor cells. Chemotherapy also damages normal cells, leading to side effects such as hair loss, vomiting, mouth sores, loss of appetite, and fatigue.

Some patients with incurable metastatic cancer of the liver can have their lives prolonged for a few months by chemotherapy. If the tumor cannot be removed by surgery, a tube (catheter) can be placed in the main artery of the liver and an implantable infusion pump can be installed (hepatic artery infusion). The pump allows much higher concentrations of cancer drugs to be carried directly to the tumor.

Hepatocellular carcinoma is resistant to most drugs. Specific drugs such as doxorubicin and cisplatin have been proven effective against this type of cancer. Systemic chemotherapy can also be used to treat liver cancer. Systemic chemotherapy does not, however, significantly lengthen the patient's survival time.

Radiation therapy

Radiation therapy is the use of high-energy rays or x rays to kill cancer cells or to shrink tumors. In liver cancer, however, radiation is only able to give brief relief from some of the symptoms, including pain. Liver cancers are not sensitive to levels of radiation considered safe for surrounding tissues. Radiation therapy has not been shown to prolong the life of a patient with liver cancer.

Liver transplantation

Removal of the entire liver (total hepatectomy) and liver transplantation are used very rarely in treating liver cancer as of 1998. This is because very few patients are eligible for this procedure, either because the cancer has spread beyond the liver or because there are no suitable donors. Further research in the field of transplant immunology may make liver transplantation a possible treatment method for more patients in the future.

Future treatments

Gene therapy may be a future treatment for liver cancer. As of 2001, scientists are still investigating the possible use of gene therapy as a treatment for cancer. As of 2001, there is controversy surrounding experimentation with gene therapy on humans. As such, it may be years before science is able to create a clinically available gene therapy treatment.

Prognosis

Liver cancer has a very poor prognosis because it is often not diagnosed until it has metastasized. Fewer than 10% of patients survive three years after the initial diagnosis; the overall five-year survival rate for patients with

hepatomas is around 4%. Most patients with primary liver cancer die within several months of diagnosis. Patients with liver cancers that metastasized from cancers in the colon live slightly longer than those whose cancers spread from cancers in the stomach or pancreas.

Prevention

There are no useful strategies at present for preventing metastatic cancers of the liver. Primary liver cancers, however, are 75–80% preventable. Current strategies focus on widespread vaccination for hepatitis B; early treatment of hereditary hemochromatosis; and screening of high-risk patients with alpha-fetoprotein testing and ultrasound examinations.

Lifestyle factors that can be modified in order to prevent liver cancer include avoidance of exposure to toxic chemicals and foods harboring molds that produce aflatoxin. In the United States laws protect workers from exposure to toxic chemicals. Changing grain storage methods in other countries may reduce aflatoxin exposure. Avoidance of alcohol and drug abuse is also very important. Alcohol abuse is responsible for 60–75% of cases of cirrhosis, which is a major risk factor for eventual development of primary liver cancer.

A vaccination for hepatitis B is now available. Widespread immunization prevents infection, reducing a person's risk for liver cancer. Other protective measures against hepatitis include using protection during sex and not sharing needles. As of 2001, scientists have found that interferon injections may lower the risk for someone with hepatitis C or cirrhosis to develop liver cancer.

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American Liver Foundation. 75 Maiden Lane, Suite 603, New York, NY 10038. (800) 465-4837 or (888) 443-7222. <http://www.liverfoundation.org>.

National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda, MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

Rebecca J. Frey, PhD
Judy C. Hawkins, MS

Long bone deficiencies associated with cleft lip/palate *see* **Roberts SC phocomelia**

Long-QT syndrome

Definition

Long-QT syndrome is a family of genetic or acquired disorders that causes cardiac arrhythmias, irregularities in the electrical activity of the heart, that can lead to cardiac arrest and sudden death. The syndrome is characterized by a longer-than-normal QT interval on an electrocardiogram.

Description

Long-QT syndrome (LQTS) is one of the sudden arrhythmia death syndromes (SADS). It is a major cause of sudden, unexplained death in children and young adults, resulting in as many as 3,000–4,000 deaths per year in the United States. Its symptoms include seizures or fainting, often in response to stress.

LQTS was first described by C. Romano and coworkers in 1963 and by O. C. Ward in 1964, as a syndrome that was almost identical to **Jervell and Lange-Nielsen syndrome**, but without congenital deafness. Therefore, LQTS also is known as Romano-Ward syndrome or Ward-Romano syndrome.

LQTS involves irregularities in the recharging of the heart's electrical system that occurs after each heartbeat or contraction. The QT interval is the period of relaxation or recovery that is required for the repolarization, or recharging, of the electrical system following each heart contraction. The depolarization that causes the heart to contract and the repolarization occur via the opening and closing of potassium, sodium, and calcium ion channels in the membranes of heart cells. As sodium channels in the heart open, positively charged sodium ions flow into

KEY TERMS

Action potential—The wave-like change in the electrical properties of a cell membrane, resulting from the difference in electrical charge between the inside and outside of the membrane.

Arrhythmia—Abnormal heart rhythm, examples are a slow, fast, or irregular heart rate.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Beta-adrenergic blocker—A drug that works by controlling the nerve impulses along specific nerve pathways.

Depolarization—The dissipation of an electrical charge through a membrane.

Electrocardiogram (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Fibrillation—A rapid, irregular heartbeat.

Ion channel—Cell membrane proteins which control the movement of ions into and out of the cell.

QT interval—The section on an electrocardiogram between the start of the QRS complex and the end of the T wave, representing the firing or depolarization of the ventricles and the period of recovery prior to repolarization or recharging for the next contraction.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

Repolarization—Period when the heart cells are at rest, preparing for the next wave of electrical current (depolarization).

Syncope—A brief loss of consciousness caused by insufficient blood flow to the brain.

Tachycardia—An excessively rapid heartbeat; a heart rate above 100 beats per minute.

Torsade de pointes—A type of tachycardia of the ventricles that is characteristic of long-QT syndrome.

the cells, making the inner surfaces of the cell membranes more positive than the outside and creating the action potential, or electrical charge. During depolarization, the sodium channels shut and, after a delay, potassium channels open and allow positively charged potassium ions to move out of the cells, returning the cell membranes to their resting state, in preparation for the next heart contraction.

Individuals with LQTS have an unusually long QT interval. If the electrical impulse for the next contraction arrives before the end of the QT recovery period, a specific arrhythmia arises in the ventricles, or lower chambers, of the heart. This arrhythmia is called polymorphous ventricular tachycardia, meaning fast heart (above 100 beats per second), or *torsade de pointes*, meaning turning of the points. A normal heartbeat begins in the right atrium of the heart and progresses down to the ventricles. In ventricular tachycardia, the heartbeat may originate in the ventricle. Usually this very fast and abnormal heartbeat reverts to normal. If it does not, it leads to ventricular fibrillation, in which the heart beats too fast, irregularly, and ineffectively. This can result in cardiac arrest and death. Variations in the QT interval from one heart cell to another also can cause arrhythmias and ventricular fibrillation in LQTS.

LQTS usually results from changes, or mutations, in one of six or more genes. These genes encode proteins that form the ion channels in the heart. Although such mutations can arise spontaneously in an individual, they are most often passed on from parent to offspring. Thus, LQTS usually runs in families.

Acquired LQTS is caused by factors other than genetic **inheritance** or mutation. Many different medications, including heart medicines, antibiotics, digestive medicines, psychiatric drugs, and anti-histamines, as well as certain poisons, can result in LQTS. Some of these drugs block potassium ion channels in the heart. Diuretic medications can cause LQTS by lowering levels of potassium, magnesium, and calcium in the blood. Mineral imbalances, resulting from chronic vomiting, diarrhea, or starvation, also can result in LQTS, as can strokes or other neurological problems or **alcoholism**. However, since only certain individuals develop LQTS under these circumstances, genetics also may play a role in the acquired disorder.

Genetic profile

Although all of the genes that are known to be involved in LQTS encode proteins that form sections or subunits of ion channels through cellular membranes, the type of LQTS depends on the specific **gene** defect.

Most forms of LQTS are autosomal dominant **genetic disorders**. Thus, the genes that cause LQTS are carried on one of the 22 pairs of autosomal **chromosomes**, rather than on the X or Y sex chromosomes. Furthermore, only one copy of the mutant gene is necessary for the development of LQTS. Thus, an individual

who inherits a normal gene copy from one parent and an abnormal gene copy from the other parent is likely to have LQTS. The children of an individual with one normal gene copy and one mutated copy have a 50% chance of inheriting LQTS.

LQT1 and LQT5

LQT1 is the most common form of LQTS. It is caused by any of a number of gene mutations in the KVLQT1 (KvLQT1) gene located on the short arm of chromosome 11. KVLQT1 also is known as KCNQ1. This gene codes for an alpha-subunit of a voltage-gated potassium ion channel that is highly expressed in the heart. Protein subunits encoded by a mutant KVLQT1 gene may combine with protein subunits encoded by a normal KVLQT1 gene to form defective potassium channels. Although most mutations in KVLQT1 are dominant, some mutations in this gene may be recessive. In these cases, LQTS is present only in individuals with two abnormal KVLQT1 genes, one inherited from each parent.

The KCNE1 (MinK or IsK) gene on chromosome 21 codes for the beta or regulatory subunit that combines with the alpha-subunit encoded by KVLQT1. Together, they form the ion channel that is responsible for the cardiac I_{Ks}) potassium current. This is a slow ion channel that is activated by depolarization of the action potential of the heart, which causes the channel to open and potassium ions to move freely out of the cells during repolarization. Mutations in KCNE1 also can cause a defective potassium channel protein, resulting in the LQT1 form of LQTS. However, LQTS resulting from mutations in KCNE1 may be called LQT5.

Jervell and Lange-Nielsen syndrome is a very rare disorder in which an individual has two copies of an abnormal KVLQT1 or KCNE1 gene, one inherited from the mother and the other from the father. This syndrome is characterized by congenital deafness as well as a prolonged QT interval.

LQT2 and LQT6

LQT2 is the second most common form of LQTS. Mutations in the HERG gene (so-named because it is the human equivalent of a fruit fly gene called ether-a-go-go) can result in LQT2. HERG, located on chromosome 7, encodes a protein subunit of another potassium ion channel in the heart. Mutations in HERG result in loss of the potassium current called I_{Kr}.

The KCNE2 or MiRP1 (for MinK-related) gene is located next to MinK (KCNE1) on chromosome 21. It encodes a regulatory beta-subunit protein that combines with the protein encoded by HERG to form a potassium ion channel. The form of LQTS resulting from mutations in the KCNE2 gene is known as LQT6.

Mutations in potassium channel genes reduce the number of functional potassium channels in the heart and lengthen the QT interval by delaying depolarization. Almost all cases of inherited LQTS result from mutations in KVLQT1 or KCNE1, causing LQT1, or mutations in HERG or KCNE2, causing LQT2.

LQT3

Mutations in the SCN5A gene can result in an uncommon form of LQTS known as LQT3. SCN5A, on chromosome 3, encodes a component of a cardiac sodium ion channel. Some mutations in this gene prevent the channel from being inactivated. Thus, although the channel opens normally and sodium ions flow into the cells with each contraction, the channel does not close properly. Sodium ions continue to leak into the cells, thereby prolonging the action potential. A different mutation in SCN5A decreases the flow of sodium ions into the cells, shortening the action potential and causing a distinct condition known as Brugada syndrome.

Other types of LQTS

Mutations in yet another gene, located on chromosome 4, can result in a type of LQTS known as LQT4.

A small number of individuals with LQTS have mutations in more than one of the known genes. Some families with inherited LQTS lack mutations in any of these known genes, suggesting the existence of other genes that can cause LQTS. Furthermore, individuals with identical LQTS genes may differ significantly in the severity of their symptoms, again suggesting the existence of other genes that can cause or modify LQTS.

Demographics

Large-scale studies of LQTS, such as the International Registry for LQTS established in 1979, have revealed that the disorder is much more prevalent than was believed originally. Inherited LQTS is estimated to occur in one out of every 5,000-10,000 individuals and it occurs in all racial and ethnic groups. LQTS may result in fetal death, may account for some cases of sudden infant death syndrome (SIDS), and has been implicated in many instances of sudden death and unexplained drownings among individuals who were previously without symptoms.

As an autosomal, non-sex-linked genetic disorder, LQTS should affect males and females in equal numbers. However, it appears to be more prevalent among women. Nearly 70% of the time, a female is the first member of a family to be recognized as having LQTS. Females are two

TABLE 1

Drugs for patients with Long QT syndrome to avoid

Drug name	Chemical name	General Use
ANESTHETICS/ASTHMA		
Adrenaline	Epinephrine	Local anesthetics, or as an asthma medication
ANTIHISTAMINES		
Seldane	Terfenadine	Allergies
Hismanal	Astemizole	Allergies
Benadryl	Diphenhydramine	Allergies
ANTIBIOTICS		
E-Mycin, EES, EryPeds, PCE etc.	Erythromycin	Infections: lung, ear, throat
Bactrim, Septra	Trimethoprim & Sulfamethoxazole	Infections: urinary, ear, lung
Pentam intravenous	Pentamidine	Lung infections
HEART MEDICATIONS		
Quinidine, Quinidex, Duraquin, Quiniqlute, etc.	Quinidine	Heart rhythm abnormalities
Pronestyl		Heart rhythm abnormalities
Norpace	Procainamide Disopyramide	Heart rhythm abnormalities
Betapace	Sotalol	Heart rhythm abnormalities
Lorelco	Probucol	High triglycerides, cholesterol
Vascor	Bepridil	Chest pain (angina)
GASTROINTESTINAL		
Propulsid	Cisapride	For esophageal reflux, acid
ANTIFUNGAL DRUGS		
Nizoral	Ketoconazole	Fungal infections
Diflucan	Fluconazole	Fungal infections
Sporanox	Itraconazole	Fungal infections
PSYCHOTROPIC DRUGS		
Elavil, Norpramine, Viractil Compazine, Stelazine,	Amitriptyline (Tricyclics)	Depression
Thorazine Mellaril, Etrafon, Trilafon, others	Phenothiazine derivatives	Mental disorders
Haldol	Haloperidol	Mental disorders
Risperdal	Risperidone	Mental disorders
ORAP	Pimozide	Mental disorders
DIURETICS		
Lozol	Indapamide	Water loss, edema
POTASSIUM LOSS		
Many diuretics cause potassium loss and low levels of potassium in the blood. Diarrhea and vomiting may have similar results, all of which aggravate symptoms of Long QT Syndrome.		

to three times more likely than males to exhibit symptoms of LQTS. However, in general, males manifest symptoms of LQTS at an earlier age than females. At puberty, the QT interval shortens in males; whereas in females it stays the same or shortens only slightly. Therefore, unaffected women have slightly longer QT intervals than unaffected men. Men with LQT1 or LQT2 have shorter QT intervals than either women or children with these two forms of the disorder. Women also are more likely than men to develop drug-induced or acquired LQTS. These gender-related differences may be due to the effects of the female hormone estrogen on the regulation of cardiac ion channels, particularly potassium channels.

Signs and symptoms

Sudden death

Tragically for many individuals with LQTS, sudden death by cardiac arrest is the first symptom. For this reason, LQTS sometimes is referred to as a "silent killer." Approximately one-third of deaths from LQTS are not preceded by any symptoms of the disease. At least one-third of the individuals carrying a gene variant that causes LQTS do not exhibit any symptoms.

SIDS is the leading cause of death among infants between the ages of one month and one year. SIDS claims the lives of one or two out of every 1,000 infants. About 7,000 babies per year die of SIDS in the United States alone. In 1998, the results of a very large study, the Multicenter Italian Study of Neonatal Electrocardiography and SIDS, conducted under the direction of Peter J. Schwartz of the University of Milan, found that a large number of SIDS victims had prolonged QT intervals.

Syncope and seizures

Dizziness, sudden loss of consciousness or fainting spells (syncopes), or convulsive seizures are common symptoms of LQTS. These occur because the heart is

unable to pump sufficient blood to the brain. Following a loss of consciousness or syncope, the torsade de pointes rhythm usually reverts spontaneously to a normal rhythm within one minute or less and the individual regains consciousness. These symptoms may appear first during infancy or early childhood, although sometimes no symptoms are evident until adulthood. Some individuals may experience syncopal episodes from childhood on; whereas others may experience one or two episodes as children, with no recurrence throughout adulthood. On average, males with LQTS first exhibit symptoms at about age eight and females at about age 14. These symptoms usually occur upon awakening, during strenuous physical activity, or during moments of excitement or stress.

Other symptoms

Newborn infants and children under the age of three with LQTS may exhibit slower than normal resting heart rates. Individuals with LQTS may experience irregular heartbeats accompanied by chest pain.

Gene-specific symptoms

Symptoms of LQTS vary depending on the specific **gene mutation**. Certain mutations in the KVLQT1 gene that cause LQT1 may result in arrhythmias when an individual is under stress. Exercise is a major trigger for cardiac events in LQT1. Swimming can trigger syncopic episodes and appears to be a gene-specific trigger in individuals with KVLQT1 mutations. Drowning is the second most common cause of accidental death in children and young adults and about 10% of such drownings are unexplained. Thus, LQT1 may account for many unexplained drownings and near-drownings.

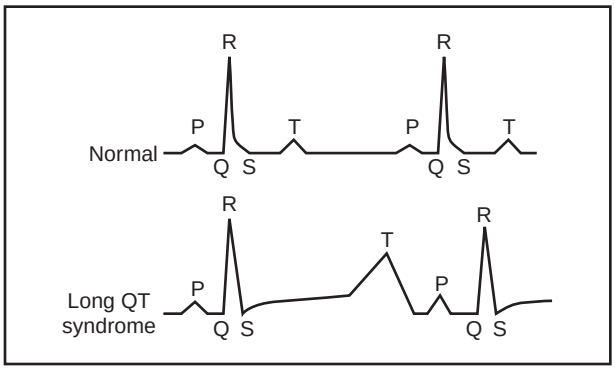
Sudden loud noises, such as telephones or alarm clocks, are more likely to trigger arrhythmias and syncopic episodes in individuals with LQT2. Cardiac events, including syncope, aborted cardiac arrest, and sudden death, are more common among individuals with LQT1 or LQT2 than among those with LQT3. However, cardiac events are more likely to be lethal in individuals with LQT3. Certain variants of the SCN5A gene that cause LQT3 result in abnormal heart rhythms during sleep.

Individuals with some of the variants of the KCNE2 gene that cause LQT6 may be adversely affected by exercise and some medications.

Diagnosis

Electrocardiogram

A diagnosis of LQTS most often comes from an electrocardiogram (ECG or EKG). An ECG records the electrical activity of the heart, using electrical leads placed at specific sites on the body. The electrical activity due to the depolarization and repolarization of the heart is recorded by each lead and added together. The recordings, on paper or on a monitor, show a series of peaks, valleys, and plateaus.



A comparison of the "QT" interval found in a normal patient versus one diagnosed with long QT syndrome obtained from an electrocardiogram. The typical QT interval is 400-440 miliseconds, but for patients with long QT syndrome the interval exceeds 460 milliseconds. This lengthened interval is obvious in the comparison above. *(Gale Group)*

The QRS complex is a sharp peak and dip on the ECG that occurs as the electrical impulses fire the cells of the ventricles, causing contraction and depolarization of the action potential. The torsade de pointes, or turning of the points, refers to these spikes in the QRS complex. Sometimes it is possible to diagnose torsade de pointes from an ECG. The T wave on the ECG occurs as the cells recover and prepare to fire again with the next heartbeat. Thus, the T-wave represents the repolarization of the ventricles. The QT interval on the ECG is the period from the start of the depolarization of the ventricles (Q), as the electrical current traverses the ventricles from the inside to the outside, through the repolarization of the ventricles (T), as the current passes from the outside to the inside. Thus, the QT interval represents the firing and recovery cycle of the ventricles. In LQTS, the QT interval on the ECG may be a few one-hundredths of a second longer than normal. A QT interval that is longer than 440 milliseconds is considered to be prolonged. There also may be abnormalities in the T-wave of the ECG.

ECGs may vary depending on the specific mutation that is the cause of the LQTS. Furthermore, as many as 12% of individuals with LQTS may have normal-appearing or borderline-normal QT intervals on an ECG. An individual's ECGs can vary, and additional ECGs or ECGs performed during exercise may reveal an abnormal QT interval. ECGs of parents or siblings also may con-

tribute to a diagnosis, since one parent, and possibly siblings, may carry a gene variation that causes LQTS and, therefore, may exhibit a prolonged QT interval on an ECG.

Other diagnostic methods

Children with LQTS may exhibit a low heart rate; specifically, a resting heart rate that is below the second percentile for their age. A fast heart rate of 140-200 beats per minute may indicate tachycardia resulting from LQTS. Convulsive seizures due to LQTS sometimes are misdiagnosed as **epilepsy**, particularly in children.

Some individuF with LQTS may have low levels of potassium in their blood.

Genetic diagnosis

Some 200 specific changes have been found in the genes that are responsible for LQTS. Furthermore, as many as one-half of the individuals diagnosed with LQTS do not carry any of the known genetic variations. Thus, it can be difficult to diagnose LQTS on the basis of **genetic testing**. However, when family members are known to carry a specific LQTS gene mutation, genetic testing may be used to diagnose LQTS in other family members.

Treatment and management

Beta-blockers

Beta-adrenergic blockers, or beta-blockers, are the most common treatment for the ventricular arrythmia resulting from LQTS. Propranolol is the most frequently prescribed drug, although nadolol also is used. Propranolol lowers the heart rate and the strength of the heart muscle contractions, thereby reducing the oxygen requirement of the heart. Propranolol also regulates abnormal heart rates and reduces blood pressure.

Beta-blockers are very effective for treating LQT1, as well as many cases of LQT2. Thus, approximately 90% of individuals with LQTS can be treated successfully with these drugs. However, since the prophylactic effects disappear within one or two days of stopping the beta-blocker, treatment with these drugs usually lasts for life. Since the first symptom of LQTS may be sudden death, younger individuals with prolonged QT intervals or with family histories of LQTS commonly are treated with beta-blockers even in the absence of symptoms.

Beta-blockers such as propranolol are considered to be safe medications. Any side effects from propranolol are usually mild and disappear once the body has adjusted to the drug. However propranolol and other beta-blockers can interact dangerously with many other medications.

Other drugs

As knowledge of the causes of LQTS increases, other drugs may prove to be more effective for treating some forms of LQTS. For example, mexiletine, a sodium-channel blocker, is used to shorten the QT interval in individuals with LQT3 that results from mutations in the SCN5A gene.

Potassium

Elevating the levels of blood potassium may relieve symptoms of LQTS in individuals with mutations in potassium channel genes. For example, increased blood potassium raises the outward potassium current in the HERG-encoded channel. Thus, treatment with potassium can compensate to some extent for the shortage of functional potassium ion channels in individuals with LQT2, thereby shortening the QT interval.

Surgical intervention

Left cardiac sympathetic denervation, the surgical cutting of a group of nerves connecting the brain and the heart, may reduce cardiac arrhythmias in individuals with LQTS. Pacemakers or automatic implanted cardioverter defibrillators (AICDs) also are used to regulate the heartbeat or to detect and correct abnormal heart rhythms. Sometimes, a pacemaker or AICD is used in combination with beta-blockers.

Preventative measures

Since the likelihood of developing symptoms of LQTS after about age 45 is quite low, individuals who are at least middle-aged when first diagnosed may not be treated. However, all individuals that have been diagnosed with LQTS must avoid reductions in blood potassium levels, such as those that occur with the use of diuretic drugs. Furthermore, individuals with LQTS must avoid a very long list of drugs and medications which can increase the QT interval or otherwise exacerbate the syndrome.

Infants in LQTS families should be screened with ECGs and monitored closely, due to the 41-fold increase in the risk of SIDS.

Individuals with LQTS usually are advised to refrain from competitive sports and to practice a “buddy” system during moderate exercise. Family members may be advised to learn cardiopulmonary resuscitation (CPR) in case of cardiac arrest.

Prognosis

The prognosis usually is quite good for LQTS patients who receive treatment. Symptoms may disappear completely and, often, at least some of the ECG abnormalities revert to normal. In contrast, the death rate for LQTS can be very high among untreated individuals.

Pregnancy

Women with LQTS usually do not experience an increase in cardiac events during pregnancy or delivery. However, they may experience an increase in serious episodes in the months following delivery. This is especially true for women who have experienced syncopic episodes prior to pregnancy. This increase in symptoms may be due to the physical and emotional stress of the postpartum period. Women who receive beta-blocker therapy during pregnancy and following delivery experience far fewer cardiac events. Beta-blockers do not appear to adversely affect a pregnancy, nor do they appear to harm the fetus.

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Cardiac Arrhythmias Research and Education Foundation, Inc. 2082 Michelson Dr., #301, Irvine, CA 92612-1212. (949) 752-2273 or (800) 404-9500. care@longqt.org. <http://www.longqt.org>.

European Long QT Syndrome Information Center. Ronnerweg 2, Nidau, 2560 Switzerland 04(132) 331-5835. jmettler @bielnews.ch. <http://www.bielnews.ch/cyberhouse/qt/qt .html>.

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Margaret Alic, PhD

Lou Gehrig disease *see* **Amyotrophiclateral sclerosis**

Lowe oculocerbrorenal syndrome *see* **Lowe syndrome**

Lowe syndrome

Definition

Lowe syndrome is a rare genetic condition that affects males. It is caused by an enzyme deficiency. It affects many body systems including the eyes, the kidneys, and the brain.

Description

Lowe syndrome was first described by Dr. Charles Lowe in 1952. The syndrome is caused by a change (mutation) in the OCRL1 **gene**. This gene is responsible for the production of the enzyme phosphatidylinositol 4,5-bisphosphate 5-phosphatase. A mutation in the OCRL1 gene leads to a decrease in enzyme activity. This decrease in the activity of phosphatidylinositol 4,5-bisphosphate 5-phosphatase is responsible for the physical and mental problems associated with Lowe syndrome. The reason why a deficiency of this enzyme causes Lowe syndrome is still unknown. Phosphatidylinositol 4,5-bisphosphate 5-phosphate phosphatase is thought to be limited to a specific part of the cell called the "Golgi apparatus." The relationship between the function of the Golgi apparatus, the enzyme deficiency, and the features of Lowe syndrome is unclear.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

Cerebro—Related to the head or brain.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Congenital—Refers to a disorder which is present at birth.

Germ line mosaicism—A rare event that occurs when one parent carries an altered gene mutation that affects his or her germ line cells (either the egg or sperm cells) but is not found in the somatic (body) cells.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nystagmus—Involuntary, rhythmic movement of the eye.

Oculo—Related to the eye.

Renal—Related to the kidneys.

Rickets—A childhood disease caused by vitamin D deficiency, resulting in soft and malformed bones.

Strabismus—An improper muscle balance of the ocular musles resulting in crossed or divergent eyes.

Another name for Lowe syndrome is oculocerebrorenal syndrome of Lowe. This name describes the body systems most commonly affected by this genetic disease. The term "oculo" refers to the eye problems commonly seen in individuals with Lowe syndrome. Cataracts (cloudiness of the lens of the eye) are a classic feature and are usually present at birth (congenital). Other eye problems are also common. The term "cerebro" refers to the brain dysfunction commonly seen in Lowe syndrome. The majority of males with Lowe syndrome have mental retardation and behavior disturbances. The term "renal" represents the kidney problems associated with Lowe syndrome. The kidney problems can interfere with normal bone development and eventually lead to kidney failure.

Genetic profile

Changes (mutations) in the OCRL1 gene decrease the activity of the enzyme phosphatidylinositol 4,5-bisphosphate 5-phosphatase. There have been many different mutations identified in the OCRL1 gene. These mutations may be different between families. The OCRL1 gene is located on the X chromosome. Since the OCRL1 gene is located on the X chromosome, Lowe syndrome is considered to be X-linked. This means that it only affects males.

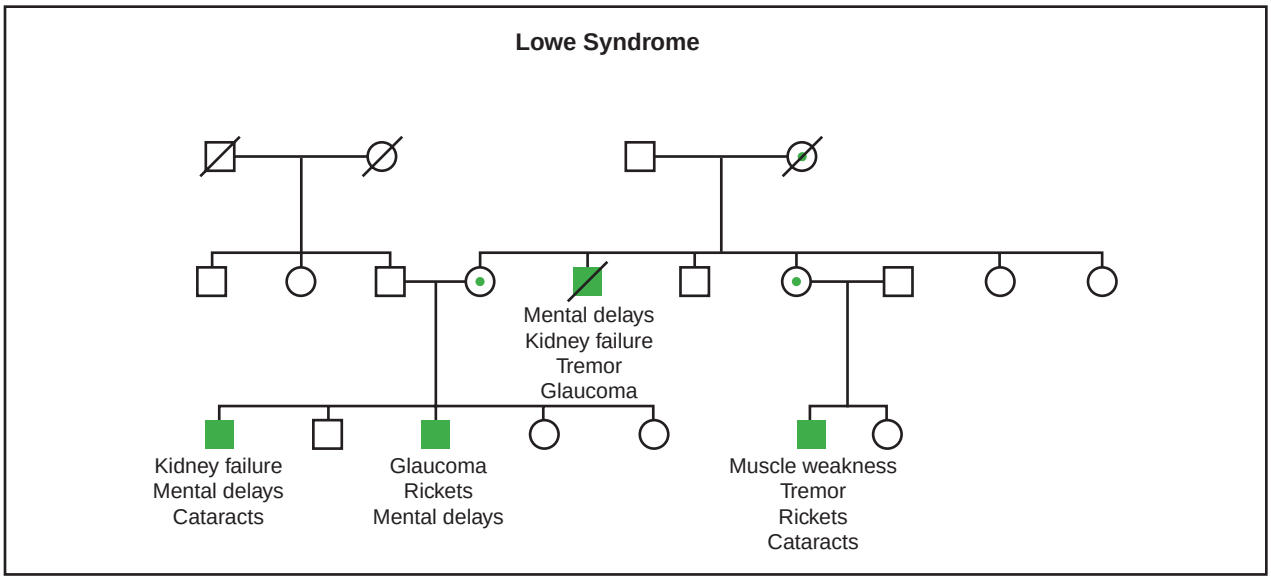
A person's sex is determined by his or her **chromosomes**. Males have one X chromosome and one Y chromosome, while females have two X chromosomes. Males who possess a mutation in their OCRL1 gene will develop Lowe syndrome. Females who possess a mutation in their OCRL1 gene will not; they are considered to be carriers. This is because females have another X chromosome without the mutation that allows normal function, and prevents them from getting this disease. If a woman is a carrier, she has a 50% risk with any pregnancy to pass on her X chromosome with the mutation. Therefore, with every male pregnancy she has a 50% risk of having an affected son, and with every female pregnancy she has a 50% risk of having a daughter who is a carrier.

Demographics

Lowe syndrome affects approximately one in 100,000 live births. It occurs evenly among ethnic groups. Almost always, only male children are affected. Women carriers usually do not have physical or mental problems related to the disease.

Signs and symptoms

The signs and symptoms of Lowe syndrome are variable. Some individuals with Lowe syndrome have many



(Gale Group)

severe symptoms, while other affected individuals have fewer, more mild symptoms.

Eye problems are a common feature of Lowe syndrome. Congenital cataracts are a classic feature of the disorder. These cataracts may be one of the first symptoms noticed during infancy. Approximately 50% of males with Lowe syndrome will develop increased pressure behind the eye (**glaucoma**). This pressure can damage the eye. Other eye problems include strabismus (crossed or divergent eyes), nystagmus (uncontrollable rhythmic eye movements), and microphthalmia (small eyes).

The nervous system (brain and nerves) is also typically affected by Lowe syndrome. Mental retardation is a common feature of Lowe syndrome. It can vary between mild and severe. Some males with Lowe syndrome have normal intelligence. Seizures and behavior disturbances can also be seen in individuals with Lowe syndrome. Behavior disturbances can include temper tantrums, aggression, obsessions, and repetitive hand movements. One of the first signs of brain dysfunction caused by Lowe syndrome is muscle weakness (hypotonia) during infancy.

Kidney problems are another common finding in individuals with Lowe syndrome. The kidneys normally filter chemicals and acids from the body. The kidneys allow the body to keep needed substances and to remove unneeded substances through the urine. Individuals with Lowe syndrome cannot do this properly, allowing needed substances (calcium, phosphate, etc.) to be excreted in the urine. This kidney disturbance can ultimately lead to kidney failure.

Individuals with Lowe syndrome frequently have slow growth and have short stature. Problems with bones can also develop due to the loss of certain substances through the kidneys. Rickets and easily breakable bones are common features. Joints may also become inflamed in individuals with Lowe syndrome.

Diagnosis

The diagnosis of Lowe syndrome is based initially on the presence of the symptoms of the disorder. Lowe syndrome is definitively diagnosed by measuring the activity of the enzyme phosphatidylinositol 4,5-bisphosphate 5-phosphatase. When the activity of this enzyme is very low it is diagnostic of Lowe syndrome. In order to perform this test a small piece of skin must be removed from the patient's body (skin biopsy). The enzyme is then measured from cells in this skin sample. In some cases it is also possible to look for a mutation in the OCRL1 gene. The presence of mutation confirms the diagnosis of Lowe syndrome in males.

Determining if a woman is a carrier of Lowe syndrome can be done several different ways. Females who carry a mutation in their OCRL1 gene commonly have changes in the lens of the eye. These changes can only be detected by an ophthalmologist with a special eye examination. These changes do not cause vision problems. The eye difference seen in carriers of Lowe syndrome is best observed once females reach adulthood. Recent reports suggest that a detailed eye exam can detect 90% of carriers. In addition to eye examinations, carrier detection can also be performed with DNA testing. If the OCRL1 muta-

tion has been identified in an affected male in the family, the females in the family can undergo DNA testing.

Prenatal diagnosis is possible by measuring the activity of phosphatidylinositol 4,5-bisphosphate 5-phosphatase in fetal tissue drawn by **amniocentesis** or chorionic villus sampling (CVS). In cases where the mutation is known, DNA testing can be used in prenatal diagnosis. Fetuses should be tested if the mother is a carrier of a Lowe syndrome. A woman is at risk of being a carrier if she has a son with Lowe syndrome or someone in her family with Lowe syndrome. Any woman at risk of being a carrier can undergo testing to determine if she is at risk to have a son with Lowe syndrome.

Treatment and management

There is currently no cure for Lowe syndrome. Individuals with Lowe syndrome benefit from therapies and regular medical care. Physical therapy, occupational therapy, and speech therapy may be recommended due to developmental delays. Regular eye exams by an ophthalmologist are also recommended. Patients with Lowe syndrome should be followed by a nephrologist (kidney doctor). Dialysis may ultimately be recommended for kidney failure.

Prognosis

The life span of males with Lowe syndrome is limited by their multiple medical problems. Death by middle age is common. However, medical advances are improving the quality of life for individuals with this genetic condition.

Resources

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ORGANIZATIONS

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

Lowe Syndrome Association. 222 Lincoln St., West Lafayette, IN 47906-2732. (765) 743-3634. <http://www.lowesyndrome.org>.

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Holly Ann Ishmael, MS

Lynch cancer family syndrome *see* **Hereditary colorectal cancer**

Lynch syndrome *see* **Muir-Torre syndrome**

Lysosomal trafficking regulator *see* **Chediak-Higashi syndrome**

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Machado-Joseph disease *see* **Azorean disease**

Macular degeneration—age-related

Definition

Macular degeneration age-related (AMD) is one of the most common causes of vision loss among adults over age 55 living in developed countries. It is caused by the breakdown of the macula, a small spot located in the back of the eye. The macula allows people to see objects directly in front of them (called central vision), as well as fine visual details. People with AMD usually have blurred central vision, difficulty seeing details and colors, and they may notice distortion of straight lines.

Description

In order to understand how the macula normally functions and how it is affected by AMD, it is important to first understand how the eye works. The eye is made up of many different types of cells and tissues that all work together to send images from the environment to the brain, similar to the way a camera records images. When light enters the eye, it passes through the lens and lands on the retina, which is a very thin tissue that lines the inside of the eye. The retina is actually made up of 10 different layers of specialized cells, which allow the retina to function similarly to film in a camera, by recording images. The macula is a small, yellow-pigmented area located at the back of the eye, in the central part of the retina. The retina contains many specialized cells called photoreceptors that sense light coming into the eye and convert it into electrical messages that are then sent to the brain through the optic nerve. This allows the brain to "see" the environment.

The retina contains two types of photoreceptor cells: rod cells and cone cells. The rod cells are located primarily outside of the macula and they allow for peripheral (side) and night vision. Most of the photoreceptor cells inside of the macula, however, are the cone cells, which are responsible for perceiving color and for viewing objects directly in front of the eye (central vision). If the macula is diseased, as in AMD, color vision and central vision are altered. There are actually two different types of AMD: Dry AMD and Wet AMD.

Dry AMD

Approximately 90% of individuals with AMD have dry AMD. This condition is sometimes referred to as nonexudative, atrophic, or drusenoid macular degeneration. In this form of AMD, some of the layers of retinal cells (called retinal pigment epithelium, or RPE cells) near the macula begin to degenerate, or breakdown. These RPE cells normally help remove waste products from the cone and rod cells. When the RPE cells are no longer able to provide this "clean-up" function, fatty deposits called drusen begin to accumulate, enlarge and increase in number underneath the macula. The drusen formation can disrupt the cones and rods in the macula, causing them to degenerate or die (atrophy). This usually leads to central and color vision problems for people with dry AMD. However, some people with drusen deposits have minimal or no vision loss, and although they may never develop AMD, they should have regular eye examinations to check for this possibility. Dry AMD is sometimes called "nonexudative", because even though fatty drusen deposits form in the eye, people do not have leakage of blood or other fluid (often called exudate) in the eye. In some cases, dry AMD symptoms remain stable or worsen slowly. In addition, approximately 10% of people with dry AMD eventually develop wet AMD.

Wet AMD

Around 10% of patients with AMD have wet AMD. This form of AMD is also called subretinal neovascular-

KEY TERMS

Central vision—The ability to see objects located directly in front of the eye. Central vision is necessary for reading and other activities that require people to focus on objects directly in front of them.

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Drusen—Fatty deposits that can accumulate underneath the retina and macula, and sometimes lead to age-related macular degeneration (AMD). Drusen formation can disrupt the photoreceptor cells, which causes central and color vision problems for people with dry AMD.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Macula—A small spot located in the back of the eye that provides central vision and allows people to see colors and fine visual details.

Multifactorial inheritance—A type of inheritance pattern where many factors, both genetic and environmental, contribute to the cause.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Peripheral vision—The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

Photoreceptors—Specialized cells lining the innermost layer of the eye that convert light into electrical messages so that the brain can perceive the environment. There are two types of photoreceptor cells: rod cells and cone cells. The rod cells allow for peripheral and night vision. Cone cells are responsible for perceiving color and for central vision.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Visual acuity—The ability to distinguish details and shapes of objects.

ization, choroidal neovascularization, exudative form or disciform degeneration. Wet AMD is caused by leakage of fluid and the formation of abnormal blood vessels (called "neovascularization") in a thin tissue layer of the eye called the choroid. The choroid is located underneath the retina and the macula, and it normally supplies them with nutrients and oxygen. When new, delicate blood vessels form, blood and fluid can leak underneath the macula, causing vision loss and distortion as the macula is pushed away from nearby retinal cells. Eventually a scar (called a disciform scar) can develop underneath the macula, resulting in severe and irreversible vision loss.

Genetic profile

AMD is considered to be a complex disorder, likely caused by a combination of genetic and environmental factors. This type of disorder is caused by **multifactorial inheritance**, which means that many factors likely interact with one another and cause the condition to occur. As implied by the words "age-related", the aging process is one of the strongest risk factors for developing AMD. A number of studies have suggested that genetic susceptibility also plays an important role in the development of AMD, and it has been estimated that the brothers and sisters of people with AMD are four times more likely to also develop AMD, compared to other individuals.

Genetic factors

Determining the role that genetic factors play in the development of AMD is a complicated task for scientists. Since AMD is not diagnosed until late in life, it is difficult to locate and study large numbers of affected people in the same family. In addition, although AMD seems to run in families, there is no clear **inheritance** pattern (such as dominant or recessive) observed when examining families. However, many studies have supported the observation that inheritance plays some role in the development of AMD.

One method scientists use to locate genes that may increase a person's chance to develop multifactorial conditions like AMD is to study genes that cause similar conditions. In 1997, this approach helped researchers identify changes (mutations) in the ATP-binding cassette transporter, retina-specific (ABCR) **gene** in people diagnosed with AMD. The process began after genetic research identified changes in the ABCR gene among people with an autosomal recessive macular disease called Stargardt macular dystrophy. This condition is phenotypically similar to AMD, which means that people with Stargardt macular dystrophy and AMD have similar symptoms, such as yellow deposits in the retina and decreased central vision.

The ABCR gene maps to chromosome 1p22, and people who have Stargardt macular dystrophy have mutations in each of their two alleles (gene copies). However, the researchers who found mutations in the ABCR gene among people with AMD located only one allele with a mutation, which likely created an increased susceptibility to AMD. They concluded that people with an ABCR **gene mutation** in one allele could have an increased chance to develop AMD during their lifetime if they also had inherited other susceptibility genes, and/or had contact with environmental risk factors. Other scientists tried to repeat this type of genetic research among people with AMD in 1999, and were not able to confirm that the ABCR gene is a strong genetic risk factor for this condition. However, it is possible that the differing research results may have been caused by different research methods, and further studies will be necessary to understand the importance of ABCR gene mutations in the development of susceptibility to AMD.

In 1998, another genetic researcher reported a family in which a unique form of AMD was passed from one generation to the next. Although most families with AMD who are studied do not show an obvious inheritance pattern in their family tree, this particular family's pedigree showed an apparently autosomal dominant form of AMD. Autosomal dominant refers to a specific type of inheritance in which only one copy of a person's gene pair (i.e. one allele) needs to have a mutation in order for it to cause the disease. An affected person with an autosomal dominant condition thus has one allele with a mutation and one allele that functions properly. There is a 50% chance for this individual to pass on the allele with the mutation, and a 50% chance to pass on the working allele, to each of his or her children.

Genetic testing done on the family reported in 1998 showed that the dominant gene causing AMD in affected family members was likely located on chromosome 1q25-q31. Although the gene linked to AMD in this family and the ABCR gene are both on chromosome 1, they are located in different regions of the chromosome. This indicates that there is genetic heterogeneity among different families with AMD, meaning that different genes can lead to the same or similar disease among different families. It is also possible that although one particular gene may be the main cause of susceptibility for AMD, other genes and/or environmental factors may help alter the age of onset of symptoms or types of physical changes seen by examining the eye. Some studies have shown that other medical conditions or certain physical characteristics may be associated with an increased risk for AMD. Some of these include:

- Heart disease
- High blood pressure
- Cataracts
- Farsightedness
- Light skin and eye color

However, not all studies have found a strong relationship between these factors and AMD. Further research is needed to decipher the role that both genetic and environmental factors play in the development of this complex condition.

Environmental factors

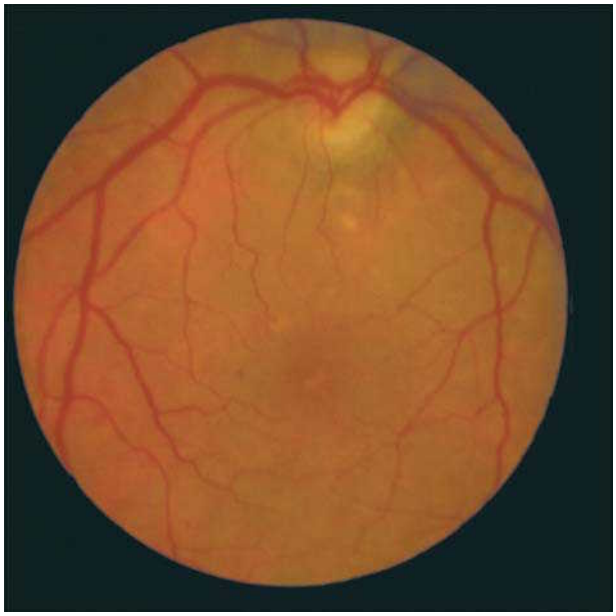
Determining the role that environmental factors play in the development of AMD is an important goal for researchers. Unlike genetic factors that cannot be controlled, people can often find motivation to change their behaviors if they are informed about environmental risk factors that may be within their control. Unfortunately, identifying environmental factors that clearly increase (or decrease) the risk for AMD is a challenging task. Several potential risk factors have been studied. These include:

- Smoking
- High fat/high cholesterol diet
- Ultraviolet (UV) exposure (sunlight)
- Low levels of dietary antioxidant vitamins and minerals

Although research has identified these possible risk factors, many of the studies have not consistently shown strong associations between these factors and the development of AMD. This makes it difficult to know the true significance of any of these risk factors. One exception, however, is the relationship between smoking and AMD. As of 1999, at least seven studies consistently found that smoking is strongly associated with AMD. This is one more important reason for people to avoid and/or quit smoking, especially if they have a family history of AMD. Further research is needed to clarify the significance of the factors listed above so people may be informed about lifestyle changes that may help decrease their risk for AMD.

Demographics

Among adults aged 55 and older, AMD is the leading cause of vision loss in developed countries. The chance to develop AMD increases with age, and although it usually affects adults during their sixth and seventh decades of life, it has been seen in some people in their forties. It is estimated that among people living in developed countries, approximately one in 2,000 are affected by AMD. By age 75, approximately 30% of people have early or mild forms of AMD, and roughly 7% have an advanced form of AMD. Since the number of people in the United States aged 65 years or older will likely dou-



A retinal photograph showing macular degeneration.
(Custom Medical Stock Photo, Inc.)

ble between 1999 and 2024, the number of people affected also should increase. Although AMD occurs in both sexes, it is slightly more common in women.

The number of people affected with AMD is different in various parts of the world and it varies between different ethnic groups. Some studies suggest that AMD is more common in Caucasians than in African Americans; however, other reports suggest the numbers of people affected in these two groups are similar. Some studies of AMD among Japanese and other Asian ethnic groups have shown an increasing number of affected individuals. Further studies are needed to examine how often AMD occurs in other ethnic groups as well.

Signs and symptoms

During eye examinations, eye care specialists may notice physical changes in the retina and macula that make them suspect the diagnosis of AMD. However, affected individuals may notice:

- Decreased visual acuity (ability to see details) of both up-close and distant objects
- Blurred central vision
- Decreased color vision
- Distorted view of lines and shapes
- A blind spot in the visual field

The majority of people with AMD maintain their peripheral vision. The severity of symptoms depends upon whether a person has dry or wet AMD. In addition, the degree of vision loss and physical symptoms that can be seen by an eye exam change over time. For example, people with dry AMD usually develop vision loss very slowly over a period of many years. Their vision may change very little from one year to the next, and they usually do not lose central vision completely. However, individuals with wet AMD usually have symptoms that worsen more quickly and they have a greater risk to develop severe central vision loss, sometimes in as little as a two-month period. Since people diagnosed with dry AMD may go on to develop wet AMD, it is important for them to take note of any changes in their symptoms and to report them to their eye care specialist.

The physical symptoms of AMD eventually impact people emotionally. One study published in 1998 reported that people with advanced stages of AMD feel they have a significantly decreased quality of life. In addition, they may have a limited ability to perform basic daily activities due to poor vision, and as a result, they often suffer psychological distress. Hopefully, improved treatment and management will eventually change this trend for affected individuals in the future.

Diagnosis

Eye care specialists use a variety of tests and examination techniques to determine if a person has AMD. Some of these include:

- Acuity testing—Involves testing vision by determining a person's ability to read letters or symbols of various sizes on an "eye chart" from a precise distance away with specific lighting present.
- Color testing—Assesses the ability of the cone cells to recognize colors by using special pictures made up of dots of colors that are arranged in specific patterns.
- Amsler grid testing—Involves the use of a grid printed on a piece of paper that helps determine the health of the macula, by allowing people to notice whether they have decreased central vision, distorted vision, or blind spots.
- Fluorescein angiography—Involves the use of a fluorescent dye, injected into the bloodstream, in order to look closely at the blood supply and blood vessels near the macula. The dye allows the eye specialist to examine and photograph the retina and macula to check for signs of wet AMD (i.e. abnormal blood vessel formation or blood leakage).

As of 2001, there are no genetic tests readily available to help diagnose AMD. Genetic research in the coming years will hopefully help scientists determine the genetic basis of AMD. This could help diagnose people

with increased susceptibility before they have symptoms, so they may benefit from early diagnosis, management and/or treatment. This knowledge may also allow people who are at a genetically increased risk for AMD to avoid environmental risk factors and thus preserve or prolong healthy vision.

Treatment and management

Treatment

There is no universal treatment available to cure either wet or dry forms of AMD. However, some people with wet AMD can benefit from laser photocoagulation therapy. This treatment involves the use of light rays from a laser to destroy the abnormal blood vessels that form beneath the retina and macula and prevent further leakage of blood and fluid. Previously lost vision cannot be restored with this treatment, and the laser can unfortunately damage healthy tissue as well, causing further loss of vision.

In April 2000, the FDA approved the use of a light-activated drug called Visudyne to help treat people with wet AMD. Visudyne is a medication that is injected into the bloodstream, and it specifically attaches to the abnormal blood vessels present under the macula in people with AMD. When light rays from a laser land on the blood vessels, the Visudyne is activated and can destroy the abnormal vessels, while causing very little damage to nearby healthy tissues. Although long term studies are needed to determine the safety and usefulness of this medication beyond two years, early reports find it an effective way to reduce further vision loss.

Researchers have been trying to identify useful treatments for dry AMD as well. Laser photocoagulation treatments are not effective for dry AMD since people with this form do not have abnormal blood or fluid leakage. Although many drugs have been tested, most have not improved visual acuity. However, one study published in October 2000, reported that people with dry AMD who received a medication called Iloprost over a six-month period noted improvements in visual acuity, daily living activities and overall quality of life. Follow-up studies will be needed to determine how safe and useful this medication will be over time.

Management

Although no treatments can cure AMD, a number of special devices can help people make the most of their remaining vision. Some of these include:

- Walking canes
- Guide dogs
- Audiotapes
- Magnifying lenses
- Telescopes
- Specialized prisms
- Large print books
- Reading machines
- Computer programs that talk or enlarge printed information

People with AMD may also find it useful to meet with low-vision specialists who can help them adapt to new lifestyle changes that may assist with daily living. Eye care specialists can help people locate low-vision specialists. There are also a number of nationwide and international support groups available that provide education and support for individuals and families affected by AMD.

Prognosis

People can live many years with AMD, although the physical symptoms and emotional side effects often change over time. The vision problems caused by dry AMD typically worsen slowly over a period of years, and people often retain the ability to read. However, for people who develop wet AMD, the chance to suddenly develop severe loss of central vision is much greater. Regular monitoring of vision by people with AMD (using an Amsler grid) and by their eye care specialists, may allow for early treatment of leaky blood vessels, therefore reducing the chance for severe vision loss. As physical symptoms worsen, people are more likely to suffer emotionally due to decreasing quality of life and independence. However, many low-vision devices and various support groups can often provide much needed assistance to help maintain and/or improve quality of life.

Resources

BOOKS

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AMD Alliance International. PO Box 550385, Atlanta, GA 30355. (877) 263-7171. <http://www.amdalliance.org>.

American Macular Degeneration Foundation. PO Box 515, Northampton, MA 01061-0515. (413) 268-7660. <http://www.macular.org>.

Foundation Fighting Blindness Executive Plaza 1, Suite 800, 11350 McCormick Rd., Hunt Valley, MD 21031. (888) 394-3937. <http://www.blindness.org>.

Macular Degeneration Foundation. PO Box 9752, San Jose, CA 95157. (888) 633-3937. <http://www.eyesight.org>.

Retina International. Ausstellungsstrasse 36, Zürich, CH-8005. Switzerland (+41 1 444 10 77). <http://www.retina-international.org>.

Pamela J. Nutting, MS, CGC

Madelung deformity *see* **Leri-Weill dyschondrosteosis**

Maffuci disease *see* **Chondrosarcoma**

Major histocompatibility complex

Definition

In humans, the proteins coded by the genes of the major histocompatibility complex (MHC) include human leukocyte antigens (HLA), as well as other proteins. HLA proteins are present on the surface of most of the body's cells and are important in helping the immune system distinguish 'self' from 'non-self'.

Description

The function and importance of MHC is best understood in the context of a basic understanding of the function of the immune system. The immune system is responsible for distinguishing 'self' from 'non-self', primarily with the goal of eliminating foreign organisms and other invaders that can result in disease. There are several levels of defense characterized by the various stages and types of immune response.

Natural immunity

When a foreign organism enters the body, it is encountered by the components of the body's natural immunity. Natural immunity is the non-specific first-line of defense carried out by phagocytes, natural killer cells, and components of the complement system. Phagocytes are specialized white blood cells capable of engulfing and killing an organism. Natural killer cells are also specialized white blood cells that respond to **cancer** cells and certain viral infections. The complement system is a group of proteins called the class III MHC that attack antigens. Antigens consist of any molecule capable of triggering an immune response. Although this list is not exhaustive, antigens can be derived from toxins, protein, carbohydrates, **DNA**, or other molecules from viruses, bacteria, cellular parasites, or cancer cells.

Acquired immunity

The natural immune response will hold an infection at bay as the next line of defense mobilizes through acquired, *or* specific immunity. This specialized type of immunity is usually needed to eliminate an infection and is dependent on the role of the proteins of the major histocompatibility complex. There are two types of acquired immunity. *Humoral immunity* is important in fighting infections outside the body's cells, such as those caused by bacteria and certain viruses. Other types of viruses and parasites that invade the cells are better fought by *cellular immunity*. The major players in acquired immunity are the antigen-presenting cells (APCs), B-cells, their secreted antibodies, and the T-cells. Their functions are described in detail below.

Humoral immunity

In humoral immunity, antigen-presenting cells, including some B-cells, engulf and break down foreign organisms. Antigens from these foreign organisms are then brought to the outside surface of the antigen-presenting cells and presented in conjunction with class II MHC proteins. The helper T-cells recognize the antigen presented in this way and release cytokines, proteins that signal B-cells to take further action. B-cells are specialized white blood cells that mature in the bone marrow. Through the process of maturation, each B-cell develops the ability to recognize and respond to a specific antigen. Helper T-cells aid in stimulating the few B-cells that can recognize a particular foreign antigen. B-cells that are stimulated in this way develop into plasma cells, which secrete antibodies specific to the recognized antigen. Antibodies are proteins that are present in the circulation, as well as being bound to the surface of B-cells. They can destroy the foreign organism from which the antigen came. Destruction occurs either directly, or by 'tagging' the organism, which will then be more easily recognized and targeted by phagocytes and complement proteins. Some of the stimulated B-cells go on to become memory

cells, which are able to mount an even faster response if the antigen is encountered a second time.

Cellular immunity

Another type of acquired immunity involves killer T-cells and is termed celluar immunity. T-cells go through a process of maturation in the organ called the thymus, in which T-cells that recognize 'self' antigens are eliminated. Each remaining T-cell has the ability to recognize a single, specific, 'non-self' antigen that the body may encounter. Although the names are similar, killer T-cells are unlike the non-specific natural killer cells in that they are specific in their action. Some viruses and parasites quickly invade the body's cells, where they are 'hidden' from antibodies. Small pieces of proteins from these invading viruses or parasites are presented on the surface of infected cells in conjunction with class I MHC proteins, which are present on the surface of most all of the body's cells. Killer T-cells can recognize antigen bound to class I MHC in this way, and they are prompted to release chemicals that act directly to kill the infected cell. There is also a role for helper T-cells and antigen-presenting cells in cellular immunity. Helper T-cells release cytokines, as in the humoral response, and the cytokines stimulate killer T-cells to multiply. Antigen-presenting cells carry foreign antigen to places in the body where additional killer T-cells can be alerted and recruited.

The major histocompatibility complex clearly performs an important role in functioning of the immune system. Related to this role in disease immunity, MHC is important in organ and tissue transplantation, as well as playing a role in susceptibility to certain diseases. HLA typing can also provide important information in parentage, forensic, and anthropologic studies. These various roles and the practical applications of HLA typing are discussed in greater detail below.

Genetic profile

Present on chromosome 6, the major histocompatibility complex consists of more than 70 genes, classified into class I, II, and III MHC. There are multiple alleles, or forms, of each HLA **gene**. These alleles are expressed as proteins on the surface of various cells in a co-dominant manner. This diversity is important in maintaining an effective system of specific immunity. Altogether, the MHC genes span a region that is four million base pairs in length. Although this is a large region, 99% of the time these closely-linked genes are transmitted to the next generation as a unit of MHC alleles on each chromosome 6. This unit is called a haplotype.

Class I

Class I MHC genes include HLA-A, HLA-B, and HLA-C. Class I MHC are expressed on the surface of almost all cells. They are important for displaying antigen from viruses or parasites to killer T-cells in cellular immunity. Class I MHC is also particularly important in organ and tissue rejection following transplantation. In addition to the portion of class I MHC coded by the genes on chromosome 6, each class I MHC protein also contains a small, non-variable protein component called *beta-2 microglobulin* coded by a gene on chromosome 15. Class I HLA genes are highly polymorphic, meaning there are multiple forms, or alleles, of each gene. There are at least 57 HLA-A alleles, 111 HLA-B alleles, and 34 HLA-C alleles.

Class II

Class II MHC genes include HLA-DP, HLA-DQ, and HLA-DR. Class II MHC are particularly important in humoral immunity. They present foreign antigen to helper T-cells, which stimulate B-cells to elicit an antibody response. Class II MHC is only present on antigen presenting cells, including phagocytes and B-cells. Like class I MHC, there are hundreds of alleles that make up the class II HLA **gene pool**.

Class III

Class III MHC genes include the complement system (i.e. C2, C4a, C4b, Bf). Complement proteins help to activate and maintain the inflammatory process of an immune response.

Demographics

There is significant variability of the frequencies of HLA alleles among ethnic groups. This is reflected in anthropologic studies attempting to use HLA-types to determine patterns of migration and evolutionary relationships of peoples of various ethnicity. Ethnic variation is also reflected in studies of HLA-associated diseases. Generally speaking, populations that have been subject to significant patterns of migration and assimilation with other populations tend to have a more diverse HLA gene pool. For example, it is unlikely that two unrelated individuals of African ancestry would have matched HLA types. Conversely, populations that have been isolated due to geography, cultural practices, and other historical influences may display a less diverse pool of HLA types, making it more likely for two unrelated individuals to be HLA-matched.

Testing

Organ and tissue transplantation

There is a role for HLA typing of individuals in various settings. Most commonly, HLA typing is used to establish if an organ or tissue donor is appropriately matched to the recipient for key HLA types, so as not to

elicit a rejection reaction in which the recipient's immune system attacks the donor tissue. In the special case of bone marrow transplantation, the risk is for graft-versus-host disease (GVHD), as opposed to tissue rejection. Because the bone marrow contains the cells of the immune system, the recipient effectively receives the donor's immune system. If the donor immune system recognizes the recipient's tissues as foreign, it may begin to attack, causing the inflammation and other complications of GVHD. As advances occur in transplantation medicine, HLA typing for transplantation occurs with increasing frequency and in various settings.

Disease susceptibility

There is an established relationship between the **inheritance** of certain HLA types and susceptibility to specific diseases. Most commonly, these are diseases that are thought to be autoimmune in nature. Autoimmune diseases are those characterized by inflammatory reactions that occur as a result of the immune system mistakenly attacking 'self' tissues. The basis of the HLA association is not well understood, although there are some hypotheses. Most autoimmune diseases are characterized by the expression of class II MHC on cells of the body that do not normally express these proteins. This may confuse the killer T-cells, which respond inappropriately by attacking these cells. *Molecular mimicry* is another hypothesis. Certain HLA types may 'look like' antigen from foreign organisms. If an individual is infected by such a foreign virus or bacteria, the immune system mounts a response against the invader. However, there may be a 'cross-reaction' with cells displaying the HLA type that is mistaken for foreign antigen. Whatever the underlying mechanism, certain HLA-types are known factors that increase the relative risk for developing specific autoimmune diseases. For example, individuals who carry the HLA B-27 allele have a relative risk of 77–90 for developing ankylosing spondylitis—meaning such an individual has a 77- to 90-fold chance of developing this form of spinal and pelvic arthritis, as compared to someone in the general population. Selected associations are listed below, together with the approximate corresponding relative risk of disease.

In addition to autoimmune disease, HLA-type less commonly plays a role in susceptibility to other diseases, including cancer, certain infectious diseases, and metabolic diseases. Conversely, some HLA-types confer a protective advantage for certain types of infectious disease. In addition, there are rare immune deficiency diseases that result from inherited mutations of the genes of components of the major histocompatibility complex.

TABLE 1

HLA disease associations

Disease	MHC allele	Approximate relative risk
Ankylosing spondylitis	B27	77–90
Celiac disease	DR3 + DR7	5–10
Diabetes, Type 1	DR3	5
Diabetes, Type 1	DR4	5–7
Diabetes, Type 1	DR3 + DR4	20–40
Graves disease	DR3	5
Hemochromatosis	A3	6–20
Lupus	DR3	1–3
Multiple sclerosis	DR2	2–4
Myasthenia gravis	B8	2.5–4
Psoriasis vulgaris	Cw6	8
Rheumatoid arthritis	DR4	3–6

The relative risks indicated in this table refer to the increased chance of a patient with an MHC allele to develop a disorder as compared to an individual without one. For example, a patient with DR4 is three to six times more likely to have rheumatoid arthritis and five to seven times more likely to develop type 1 diabetes than an individual without the DR4 allele.

Parentage

Among other tests, HLA typing can sometimes be used to determine parentage, most commonly paternity, of a child. This type of testing is not generally done for medical reasons, but rather for social or legal reasons.

Forensics

HLA-typing can provide valuable DNA-based evidence contributing to the determination of identity in criminal cases. This technology has been used in domestic criminal trials. Additionally, it is a technology that has been applied internationally in the human-rights arena. For example, HLA-typing had an application in Argentina following a military dictatorship that ended in 1983. The period under the dictatorship was marked by the murder and disappearance of thousands who were known or suspected of opposing the regime's practices. Children of the disappeared were often 'adopted' by military officials and others. HLA-typing was one tool used to determine non-parentage and return children to their biological families.

Anthropologic studies

HLA-typing has proved to be an invaluable tool in the study of the evolutionary origins of human populations. This information, in turn, contributes to an under-

standing of cultural and linguistic relationships and practices among and within various ethnic groups.

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Jennifer Denise Bojanowski, MS, CGC

Male turner syndrome *see* **Noonan syndrome**

Malignant fever *see* **Malignant hyperthermia**

Malignant hyperpyrexia *see* **Malignant hyperthermia**

Malignant hyperthermia

Definition

Malignant hyperthermia (MH) is a condition that causes a number of physical changes to occur among genetically susceptible individuals when they are exposed to a particular muscle relaxant or certain types of medications used for anesthesia. The changes may include increased rate of breathing, increased heart rate, muscle stiffness, and significantly increased body temperature (i.e. hyperthermia). Although MH can usually be treated successfully, it sometimes leads to long-term physical illness or death. Research has identified a number of genetic regions that may be linked to an increased MH susceptibility.

Description

Unusual response to anesthesia was first reported in a medical journal during the early 1960s, when physicians described a young man in need of urgent surgery for a serious injury. He was very nervous about exposure to anesthesia, since he had 10 close relatives who died during or just after surgeries that required anesthesia. The patient himself became very ill and developed a high temperature after he was given anesthesia. During the next decade, more cases of similar reactions to anesthesia were reported, and specialists began using the term *malignant hyperthermia* to describe the newly recognized condition. The word hyperthermia was used because people with this condition often rapidly develop a very high body temperature. The word malignant referred to the fact that the majority (70–80%) of affected individuals died. The high death rate in the 1960s occurred because the underlying cause of the condition was not understood, nor was there any known treatment (other than basically trying to cool the person's body with ice).

Increased awareness of malignant hyperthermia and scientific research during the following decades improved medical professionals' knowledge about what causes the condition, how it affects people, and how it should be treated. MH can be thought of as a chain reaction that is triggered when a person with MH susceptibility is exposed to specific drugs commonly used for anesthesia and muscle relaxation.

Triggering drugs that may lead to malignant hyperthermia include:

- halothane
- enflurane
- isoflurane
- sevoflurane
- desflurane
- methoxyflurane
- ether
- succinylcholine

Once an MH susceptible person is exposed to one or more of these anesthesia drugs, they can present with a variety of signs. One of the first clues that a person is susceptible to MH is often seen when they are given a mus-

cle relaxant called succinyl choline. This drug generally causes some stiffness in the masseter (jaw) muscles in most people. However, individuals with MH susceptibility can develop a much more severe form of jaw stiffness called *masseter spasm* when they receive this drug. They may develop muscle stiffness in other parts of their bodies as well. When exposed to any of the trigger drugs listed above (inhalants for anesthesia), people with MH susceptibility can develop an increased rate of metabolism in the cells of their body, resulting in rapid breathing, rapid heartbeat, high body temperature (over 110°F), muscle stiffness, and muscle breakdown. If these signs are not recognized, treated, or able to be controlled, brain damage or death can occur due to internal bleeding, heart failure, or failure other organs.

The series of events that occur after exposure to trigger drugs is activated by an abnormally high amount of calcium inside muscle cells. This is due to changes in the chemical reactions that control muscle contraction and the production of energy. Calcium is normally stored in an area called the sarcoplasmic reticulum, which is a system of tiny tubes located inside muscle cells. This system of tubes allows muscles to contract (by releasing calcium) and to relax (by storing calcium) in muscle cells. Calcium also plays an important role in the production of energy inside cells (i.e. metabolism). There are at least three important proteins located in (or nearby) the sarcoplasmic reticulum that control how much calcium is released into muscle cells and thus help muscles contract. One of these proteins is a "calcium release channel" protein that has been named the *ryanodine receptor protein*, or RYR. This protein (as well as the **gene** that tells the body how to make it) has been an important area of research. For some reason, when people with MH susceptibility are exposed to a trigger drug, they can develop very high levels of calcium in their muscle cells. The trigger drugs presumably stimulate the proteins that control the release of calcium, causing them to create very high levels of calcium in muscle cells. This abnormally high calcium level then leads to increased metabolism, muscle stiffness, and the other symptoms of MH.

The amount of time that passes between the exposure to trigger drugs and the appearance of the first symptoms of MH varies between different people. Symptoms begin within 10 minutes for some individuals, although several hours may pass before symptoms appear in others. This means that some people do not show signs of MH until they have left the operating room and are recovering from surgery. In addition, some individuals who inherit MH susceptibility may be exposed to trigger drugs numerous times during multiple surgeries without any complications. However, they still have an increased risk to develop an MH episode during future exposures.

KEY TERMS

Anesthesia—Lack of normal sensation (especially to pain) brought on by medications just prior to surgery or other medical procedures.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Hyperthermia—Body temperature that is much higher than normal (i.e. higher than 98.6°F).

Masseter spasm—Stiffening of the jaw muscles. Often one of the first symptoms of malignant hyperthermia susceptibility that occurs after exposure to a trigger drug.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Sarcoplasmic reticulum—A system of tiny tubes located inside muscle cells that allow muscles to contract and relax by alternatively releasing and storing calcium.

Trigger drugs—Specific drugs used for muscle relaxation and anesthesia that can trigger an episode of malignant hyperthermia in a susceptible person. The trigger drugs include halothane, enflurane, isoflurane, sevoflurane, desflurane, methoxyflurane, ether, and succinylcholine.

This means that people who have an increased risk for MH susceptibility due to their family history cannot presume they are not at risk simply because they previously had successful surgeries. Although MH was frequently a fatal condition in the past, a drug called dantrolene sodium became available in 1979, which greatly decreased the rate of both death and disability.

Genetic profile

Susceptibility to MH is generally considered to be inherited as an autosomal dominant trait. "Autosomal" means that males and females are equally likely to be affected. "Dominant" refers to a specific type of **inheritance** in which only one copy of a person's gene pair needs to be changed in order for the susceptibility to be present. In this situation, an individual susceptible to MH receives a changed copy of the same gene from one parent (who is also susceptible to MH). This means that a person with MH susceptibility has one copy of the changed gene and one copy of the gene that works well. The chance that a parent with MH susceptibility will

have a child who is also susceptible is 50% for each pregnancy. The same parent would also have a 50% chance to have a non-susceptible child with each pregnancy.

It is not unusual for people to not know they inherited a genetic change that causes MH susceptibility. This is because they typically do not show symptoms unless they are exposed to a specific muscle relaxant or certain anesthetics, which may not be needed by every person during his or her lifetime. In addition, people who inherit MH susceptibility do not always develop a reaction to trigger drugs, which means their susceptibility may not be recognized even if they do have one or more surgeries. Once MH susceptibility is diagnosed in an individual, however, it is important for his or her family members to know they also have a risk for MH susceptibility, since it is a dominant condition. This means that anyone with a family member who has MH susceptibility should tell their doctor about their family history. Since MH may go unrecognized, it is important that anyone who has had a close relative die from anesthesia notify the anesthesiologist before any type of surgery is planned. People with a family history of MH susceptibility may choose to meet with a genetic counselor to discuss the significance of their family history as well. In addition, relatives of an affected person may consider having a test to see if they also inherited MH susceptibility.

Although there are many people who have the same symptoms of MH when exposed to trigger drugs, genetic research has shown that there are probably many genes, located on different **chromosomes**, that can all lead to MH susceptibility. This indicates that there is genetic heterogeneity among different families with MH susceptibility, meaning that different genes can lead to the same or similar disease among different families. As of March 2001, researchers identified six different types of MH susceptibility. Although specific genes have been discovered for some of these types, others have been linked only to specific chromosomal regions.

Genetic classification of malignant hyperthermia:

- MHS1—Located on chromosome 19q13.1. Specific gene called RYR1. Gene creates the RYR protein.
- MHS2—Located on chromosome 17q11.2-24. Suspected gene called SCN4A.
- MHS3—Located on chromosome 7q21-22. Suspected gene called CACNA2DI. Gene creates part of the DHPR protein called the alpha 2/delta subunit.
- MHS4—Located on chromosome 3q13.1. Specific gene and protein unknown.
- MHS5—Located on chromosome 1q32. Specific gene called CACNA1S. Gene creates part of the DHPR protein called the alpha 1 subunit.
- MHS6—Located on chromosome 5p. Specific gene and protein unknown.

Over half of all families with MH susceptibility are believed to have MHS1 (i.e. have changes in the RYR1 gene), while the rest have MHS2, MHS3, MHS4, MHS5, or MHS6. However, as of January 2000, only 20% of all families tested had specific genetic changes identified in the RYR1 gene. This is because there are many different types of genetic changes in the gene that can all lead to MH susceptibility, and many families have changes that are unique. As a result, **genetic testing** of the RYR1 gene is complicated, time consuming, and often cannot locate all possible genetic changes. In addition, genetic testing for families may become more complex as knowledge about MH grows. This issue was discussed in an article published by researchers in July 2000. The authors explained that although MH susceptibility has typically been described as an autosomal dominant trait caused by a single gene that is passed from one generation to the next, they believe MH susceptibility may actually depend upon various genetic changes that occur in more than one gene. Further research may clarify this issue in the future.

While specific genes have been identified for some of the MH susceptibility types (i.e. RYR1 and DHPR alpha 1 subunit), not all changes in these genes lead specifically to MH susceptibility. For example, although at least 20 different genetic changes have been identified in the RYR1 gene that can lead to MH susceptibility, some people who have certain types of these changes actually have a different genetic condition that affects the muscles called **central core disease** (CCD). Infants with this autosomal dominant condition typically have very poor muscle tone (i.e. muscle tension) as well as an increased susceptibility to MH. Among families who have CCD, there are some individuals who do not have the typical muscle changes, but have MH susceptibility instead. Hopefully, future research will help scientists understand why the same genetic change in the RYR1 gene can cause different symptoms among people belonging to the same family.

Demographics

The exact number of individuals who are born with a genetic change that causes MH susceptibility is not known. Until genetic research and genetic testing improves, this number will likely remain unclear. However, it is estimated that internationally one in 50,000 people who are exposed to anesthesia develop an MH reaction. Among children, it is estimated that one in 5,000 to one in 15,000 develop MH symptoms when exposed to anesthesia. MH has been seen in many countries, although there are some geographic areas where it

occurs more often in the local populations, including parts of Wisconsin, North Carolina, Austria, and Quebec.

Signs and symptoms

Although the specific symptoms of malignant hyperthermia can vary, the most common findings include:

- stiffness/spasms of jaw muscles and other muscles
- rapid breathing, causing decreased oxygen and increased carbon dioxide in the blood
- rapid or irregular heartbeat
- high body temperature (over 110°F)
- muscle breakdown (may cause dark or cola-colored urine)
- internal bleeding, kidney failure, brain damage, or death (if not treated successfully)

Diagnosis

The diagnosis of MH susceptibility can be made before or during a reaction to a triggering drug. Ideally, the diagnosis is made before a susceptible individual is exposed and/or develops a reaction. This is possible for people who learn they have an increased chance for MH because they have a relative with MH susceptibility. Testing these individuals requires a surgical procedure called a muscle biopsy, in which a piece of muscle tissue is removed from the body (usually from the thigh). Safe (i.e. non-triggering) anesthetics are used during the procedure. The muscle is taken to a laboratory and is exposed to halothane (a triggering anesthetic) and caffeine, both of which cause any muscle tissue to contract, or tighten. Thus the test is called the caffeine halothane contracture test (CHCT). Muscle tissue taken from individuals with MH susceptibility is more sensitive to caffeine and halothane, causing it to contract more strongly than normal muscle tissue from non-susceptible people. This type of test is a very accurate way to predict whether a person has MH susceptibility or not. However, the test does require surgery, time to recover (typically three days), and it is expensive (approximately $2,500). In the United States, many insurance companies will pay for the testing if it is needed. Although the test is not available in every state or country, there are at least 40 medical centers worldwide that can perform the test.

Unfortunately, not all MH susceptible people will learn from their family histories that they have an increased risk for MH before they are exposed to a trigger drug. For these individuals, the diagnosis of MH susceptibility is often made during surgery by the anesthesiologist (a physician specializing in anesthesia) who is providing the anesthesia medications. Other health care specialists also may notice symptoms of MH during or after surgery. Symptoms such as rapid breathing, rapid heart rate, and high body temperature can usually be detected with various machines or devices that examine basic body functions during surgery. Muscle stiffness of the jaw, arms, legs, stomach and chest may be noticed as well. These symptoms may happen during surgery or even several hours later. If the diagnosis is made during or after surgery, immediate treatment is needed to prevent damage to various parts of the body or death. If a person has a suspicious reaction to anesthesia, he or she may undergo a muscle biopsy to confirm MH susceptibility at a later date.

In spite of the fact that a number of important genes and genetic regions associated with MH susceptibility have been identified, testing a person's **DNA** for all of the possible changes that may cause this condition is not easily done for affected individuals and their families. As of March 2001, existing genetic testing identifies some changes that have been seen among families with MHS1 and MHS6. Research studies may provide information for families with MHS2, MHS3, MHS4, and MHS5 as well. Sometimes the testing requires DNA from only one affected person, but in other cases, many samples are needed from a variety of family members. However, until genetic technology improves, the contracture test that is done on muscle tissue will likely remain the "gold standard" for diagnosis of MH susceptibility.

Treatment and management

The early identification of an MH episode allows for immediate treatment with an "antidote" called dantrolene sodium. This medication prevents the release of calcium from the sarcoplasmic reticulum, which decreases muscle stiffness and energy production in the cells. If hyperthermia develops, the person's body can be cooled with ice. In addition, the anesthesiologist will change the anesthetic from a trigger drug to a non-trigger drug. Immediate treatment is necessary to prevent serious illness and/or death.

Once a person with definite or suspected MH susceptibility is diagnosed (by an MH episode, muscle biopsy, or family history), prevention of an MH episode is possible. There are many types of non-triggering anesthetic drugs and muscle relaxants that can be used during surgical procedures. The important first step in this process is for people with known or suspected MH susceptibility to talk with their doctors before any surgery, so that only non-triggering drugs are used. People with definite or suspected MH susceptibility should always carry some form of medical identification that describes their diagnosis in

case emergency surgery is needed. The Malignant Hyperthermia Association of the United States provides wallet-sized emergency medical ID cards for its members.

Prognosis

Early diagnosis and treatment of MH episodes with dantrolene sodium has dramatically improved the prognosis for people who develop MH during or just after surgery. When the condition was first recognized in the 1960s, no real treatment (other than cooling the person's body) was available, and only 20–30% of people who developed MH survived. When the antidote (dantrolene sodium) became available in 1979, the survival rate increased to 70–80%. However, 5–10% of people who develop MH after exposure to a trigger drug still may die even with proper medication and care. Among those who do survive, some are disabled due to kidney, muscle, or brain damage. The best prognosis exists for people with definite or suspected MH susceptibility who are able to prevent exposures to trigger drugs by discussing their history with their doctors. Improved genetic testing in the future may help identify most or all people with inherited MH susceptibility, so they too may prevent exposures that could trigger MH episodes.

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Pamela J. Nutting, MS, CGC

Manic-depressive psychosis *see* **Bipolar disorder**

Mannosidosis

Definition

Mannosidosis is a rare inherited disorder, an inborn error of metabolism, that occurs when the body is unable to break down chains of a certain sugar (mannose) properly. As a result, large amounts of sugar-rich compounds build up in the body cells, tissues, and urine, interfering with normal body functions and development of the skeleton.

Description

Mannosidosis develops in patients whose genes are unable to make an enzyme required by lysosomes (structures within the cell where proteins, sugars, and fats are broken down and then released back into the cell to make other molecules). Lysosomes need the enzyme to break down, or degrade, long chains of sugars. When the enzyme is missing and the sugar chains are not broken down, the sugars build up in the lysosomes. The lysosomes swell and increase in number, damaging the cell. The result is mannosidosis.

The enzyme has two forms: alpha and beta. Similarly, the disorder mannosidosis has two forms: alpha-mannosidosis (which occurs when the alpha form of the enzyme is missing) and beta-mannosidosis (which occurs when the beta form of the enzyme is missing). Production of each form of the enzyme is controlled by a different **gene**.

First described in 1967, alpha-mannosidosis is classified further into two types. Infantile (or Type I) alpha-mannosidosis is a severe disorder that results in mental retardation, physical deformities, and death in childhood. Adult (or Type II) alpha-mannosidosis is a milder disorder in which mental retardation and physical deformities develop much more slowly throughout the childhood and teenage years.

Beta-mannosidosis was identified nearly 20 years later in 1986. Patients with this form of the disorder are also mentally retarded but over a wide range of severity, from mild to extreme. Beta-mannosidosis is not well understood, in part because it is such a rare disease. It was discovered only because researchers searched for it: a deficiency of the beta form of the enzyme was known to cause disease in animals.

Genetic profile

The two forms of mannosidosis, alpha and beta, are caused by changes on two different genes. Mutations in the gene MANB, on chromosome 19, result in alpha-mannosidosis. This gene is also known as MAN2B1 or LAMAN. Defects in MANB cause alpha-mannosidosis in both infants and adults.

Beta-mannosidosis is caused by mutations in the gene MANB1 (also called MANBA). This gene is on chromosome 4.

Both genes, MANB and MANB1, are inherited as autosomal recessive traits. This means that if a man and woman each carry one defective gene, then 25% of their children are expected to be born with the disorder. Each gene is inherited separately from the other.

Demographics

Mannosidosis is a rare disorder, occurring in both men and women. The disorder does not affect any particular ethnic group but rather appears in a broad range of people. Alpha-mannosidosis has been studied in Scandinavian, Western and Eastern European, North American, Arabian, African, and Japanese populations. Researchers have identified beta-mannosidosis in European, Hindu, Turkish, Czechoslovakian, Jamaican-Irish, and African families.

Signs and symptoms

The various forms and types of mannosidosis all have one symptom in common: mental retardation. Other signs and symptoms vary.

Infants with alpha-mannosidosis appear normal at birth, but by the end of their first year, they show signs of mental retardation, which rapidly gets worse. They develop a group of symptoms that includes dwarfism, shortened fingers, and facial changes. In these children, the bridge of the nose is flat, they have a prominent forehead, their ears are large and low set, they have protruding eyebrows, and the jaw juts out. Other symptoms include lack of muscle coordination, enlarged spleen and liver, recurring infections, and cloudiness in the back of the eyeball, which is normally clear. These patients often have empty bubbles in their white blood cells, a sign that sugars are being stored improperly.

The adult form occurs in 10–15% of the cases of alpha-mannosidosis. The symptoms in adults are the same as in infants, but they are milder and develop more slowly. Patients with adult alpha-mannosidosis are often normal as babies and young children, when they develop mentally and physically as expected. In their childhood or teenage years, however, mental retardation and physical symptoms become evident. These patients may also lose their hearing and have pain in their joints.

Beta-mannosidosis is characterized by symptoms that range from mild to severe. In all patients, however, the most frequent signs are mental retardation, lung infections, and hearing loss with speech difficulties. In mild cases, patients have red, wart-like spots on their skin. In severe cases, patients may have multiple seizures, and their arms and legs may be paralyzed. Because the symptoms of beta-mannosidosis vary so greatly, researchers suggest that the disorder may frequently be misdiagnosed.

Diagnosis

All types of mannosidosis are tested in the same way. In an infant, child, or adult, doctors can check the patient's urine for abnormal types of sugar. They may also test the patient's blood cells to learn if the enzyme is present.

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Lysosomal storage disease—A category of disorders that includes mannosidosis.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mannose—A type of sugar that forms long chains in the body.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

If doctors suspect that a pregnant woman may be carrying a child with mannosidosis, they can test cells in the fluid surrounding the baby for enzyme activity.

Treatment and management

There is no known treatment for mannosidosis. The symptoms—mental retardation and skeletal abnormalities—are managed by supportive care, depending on the severity. Patients with adult alpha-mannosidosis and beta-mannosidosis may show mild mental retardation or behavior problems (such as **depression** or aggression) and may be mainstreamed into society. Others may require institutionalization. Skeletal abnormalities may require surgery to correct them, and recurring infections are treated with antibiotics.

Research with animals suggests that mannosidosis can be treated by placing healthy cells without defective genes into the animals' bones (bone marrow transplant). Other researchers have successfully treated mannosidosis in animals by inserting healthy genes into the unborn offspring of a pregnant animal. These treatments have not been proven on humans, however.

Prognosis

The future for patients with mannosidosis varies with the form of their disorder. For infants with alpha-mannosidosis, death is expected between ages three and 12 years. For infants with beta-mannosidosis, death will come earlier, by the time they are 15 months old.

Patients with mild forms of alpha- and beta-mannosidosis often survive into adulthood, but their lives are complicated by mental retardation and physical deterioration. They will generally die in their early or middle years, depending on the severity of their disorder.

Resources

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Michalski, Jean-Claude, and Andre Klein. "Glycoprotein Lysosomal Storage Disorders: Alpha- and Beta-Mannosidosis, Glucosidosis, and Alpha-N-Acetylgalactosaminidase Deficiency." *Biochimica et Biophysica Acta: Molecular Basis of Disease* 1455, no. 2–3 (October 8, 1999): 69–84.

ORGANIZATIONS

Arc (a National Organization on Mental Retardation). 1010 Wayne Ave., Suite 650, Silver Spring, MD 20910. (800) 433-5255. <http://www.thearclink.org>.

Children Living with Inherited Metabolic Diseases. The Quadrangle, Crewe Hall, Weston Rd., Crewe, Cheshire, CW1-6UR. UK 127 025 0221. Fax: 0870-7700-327. <http://www.climb.org.uk>.

International Society for Mannosidosis and Related Diseases. 3210 Batavia Ave., Baltimore, MD 21214. (410) 254-4903. <http://www.mannosidosis.org>.

National MPS Society. 102 Aspen Dr., Downingtown, PA 19335. (610) 942-0100. Fax: (610) 942-7188. info @mpssociety.org. <http://www.mpssociety.org>.

WEBSITES

Web Site for Rare Genetic Diseases in Children: Lysosomal Storage Diseases. <http://mcrcr2.med.nyu.edu/murphp01/lysosome/lysosome.htm>.

Linnea E. Wahl, MS

Marfan syndrome

Definition

Marfan syndrome is an inherited disorder of the connective tissue that causes abnormalities of the patient's eyes, cardiovascular system, and musculoskeletal system. It is named for the French pediatrician, Antoine Marfan (1858-1942), who first described it in 1896. Marfan syndrome is sometimes called arachnodactyly, which means "spider-like fingers" in Greek, since one of the characteristic signs of the disease is disproportionately long fingers and toes. It is estimated that one person in every 3,000-5,000 has Marfan syndrome, or about 50,000 people in the United States. Marfan syndrome is one of the more common inheritable disorders.

Description

Marfan syndrome affects three major organ systems of the body: the heart and circulatory system, the bones and muscles, and the eyes. The genetic mutation responsible for Marfan was discovered in 1991. It affects the body's production of fibrillin, which is a protein that is an important part of connective tissue. Fibrillin is the primary component of the microfibrils that allow tissues to stretch repeatedly without weakening. Because the

patient's fibrillin is abnormal, his or her connective tissues are looser than usual, which weakens or damages the support structures of the entire body.

The most common external signs associated with Marfan syndrome include excessively long arms and legs, with the patient's arm span being greater than his or her height. The fingers and toes may be long and slender, with loose joints that can bend beyond their normal limits. This unusual flexibility is called hypermobility. The patient's face may also be long and narrow, and he or she may have a noticeable curvature of the spine. It is important to note, however, that Marfan patients vary widely in the external signs of their disorder and in their severity; even two patients from the same family may look quite different. Most of the external features of Marfan syndrome become more pronounced as the patient gets older, so that diagnosis of the disorder is often easier in adults than in children. In many cases, the patient may have few or very minor outward signs of the disorder, and the diagnosis may be missed until the patient develops vision problems or cardiac symptoms.

Marfan syndrome by itself does not affect a person's intelligence or ability to learn. There is, however, some clinical evidence that children with Marfan have a slightly higher rate of **attention deficit hyperactivity disorder (ADHD)** than the general population. In addition, a child with undiagnosed nearsightedness related to Marfan may have difficulty seeing the blackboard or reading printed materials, and thus do poorly in school.

KEY TERMS

Arachnodactyly—A condition characterized by abnormally long and slender fingers and toes.

Ectopia lentis—Dislocation of the lens of the eye. It is one of the most important single indicators in diagnosing Marfan syndrome.

Fribrillin—A protein that is an important part of the structure of the body's connective tissue. In Marfan's syndrome, the gene responsible for fibrillin has mutated, causing the body to produce a defective protein.

Hypermobility—Unusual flexibility of the joints, allowing them to be bent or moved beyond their normal range of motion.

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Pectus carinatum—An abnormality of the chest in which the sternum (breastbone) is pushed outward. It is sometimes called "pigeon breast."

Pectus excavatum—An abnormality of the chest in which the sternum (breastbone) sinks inward; sometimes called "funnel chest."

Scoliosis—An abnormal, side-to-side curvature of the spine.

Genetic profile

Marfan syndrome is caused by a single **gene** for fibrillin on chromosome 15, which is inherited in most cases from an affected parent. Between 15% and 25% of cases result from spontaneous mutations. Mutations of the fibrillin gene (FBNI) are unique to each family affected by Marfan, which makes rapid genetic diagnosis impossible, given present technology. The syndrome is an autosomal dominant disorder, which means that someone who has it has a 50% chance of passing it on to any offspring.

Another important genetic characteristic of Marfan syndrome is variable expression. This term means that the mutated fibrillin gene can produce a variety of symptoms of very different degrees of severity, even in members of the same family.

Demographics

Marfan syndrome affects males and females equally, and appears to be distributed equally among all races and ethnic groups. The rate of mutation of the fibrillin gene, however, appears to be related to the age of the patient's father; older fathers are more likely to have new mutations appear in chromosome 15.

Signs and symptoms

Cardiac and circulatory abnormalities

The most important complications of Marfan syndrome are those affecting the heart and major blood vessels; some are potentially life-threatening. About 90% of Marfan patients will develop cardiac complications.

- Aortic enlargement. This is the most serious potential complication of Marfan syndrome. Because of the abnormalities of the patient's fibrillin, the walls of the aorta (the large blood vessel that carries blood away from the heart) are weaker than normal and tend to stretch and bulge out of shape. This stretching increases the likelihood of an aortic dissection, which is a tear or separation between the layers of tissue that make up the aorta. An aortic dissection usually causes severe pain in the abdomen, back, or chest, depending on the section of the aorta that is affected. Rupture of the aorta is a

medical emergency requiring immediate surgery and medication.

- Aortic regurgitation. A weakened and enlarged aorta may allow some blood to leak back into the heart during each heartbeat; this condition is called aortic regurgitation. Aortic regurgitation occasionally causes shortness of breath during normal activity. In serious cases, it causes the left ventricle of the heart to enlarge and may eventually lead to heart failure.
- Mitral valve prolapse. Between 75% and 85% of patients with Marfan syndrome have loose or "floppy" mitral valves, which are the valves that separate the chambers of the heart. When these valves do not cover the opening between the chambers completely, the condition is called mitral valve prolapse. Complications of mitral valve prolapse include heart murmurs and arrhythmias. In rare cases, mitral valve prolapse can cause sudden death.
- Infective endocarditis. Infective endocarditis is an infection of the endothelium, the tissue that lines the heart. In patients with Marfan syndrome, it is the abnormal mitral valve that is most likely to become infected.
- Other complications. Some patients with Marfan syndrome develop cystic disease of the lungs or recurrent spontaneous pneumothorax, a condition in which air accumulates in the space around the lungs. Many patients will also eventually develop emphysema.

Musculoskeletal abnormalities

Marfan syndrome causes an increase in the length of the patient's bones, with decreased support from the ligaments that hold the bones together. As a result, the patient may develop various deformities of the skeleton or disorders related to the relative looseness of the ligaments.

Disorders of the spine

- **Scoliosis**. Scoliosis, or curvature of the spine, is a disorder in which the vertebrae that make up the spine twist out of line from side to side into an S-shape or a spiral. It is caused by a combination of the rapid growth of children with Marfan, and the looseness of the ligaments that help the spine to keep its shape.
- Kyphosis is an abnormal outward curvature of the spine, sometimes called hunchback when it occurs in the upper back. Patients with Marfan may develop kyphosis either in the upper (thoracic) spine or the lower (lumbar) spine.
- Spondylolisthesis. Spondylolisthesis is the medical term for a forward slippage of one vertebra on the one below it. It produces an ache or stiffness in the lower back.
- Dural ectasia. The dura is the tough, fibrous outermost membrane covering the brain and the spinal cord. The weak dura in patients with Marfan swells or bulges under the pressure of the spinal fluid. This swelling is called ectasia. In most cases, dural ectasia occurs in the lower spine, producing low back ache, a burning feeling, or numbness or weakness in the legs.

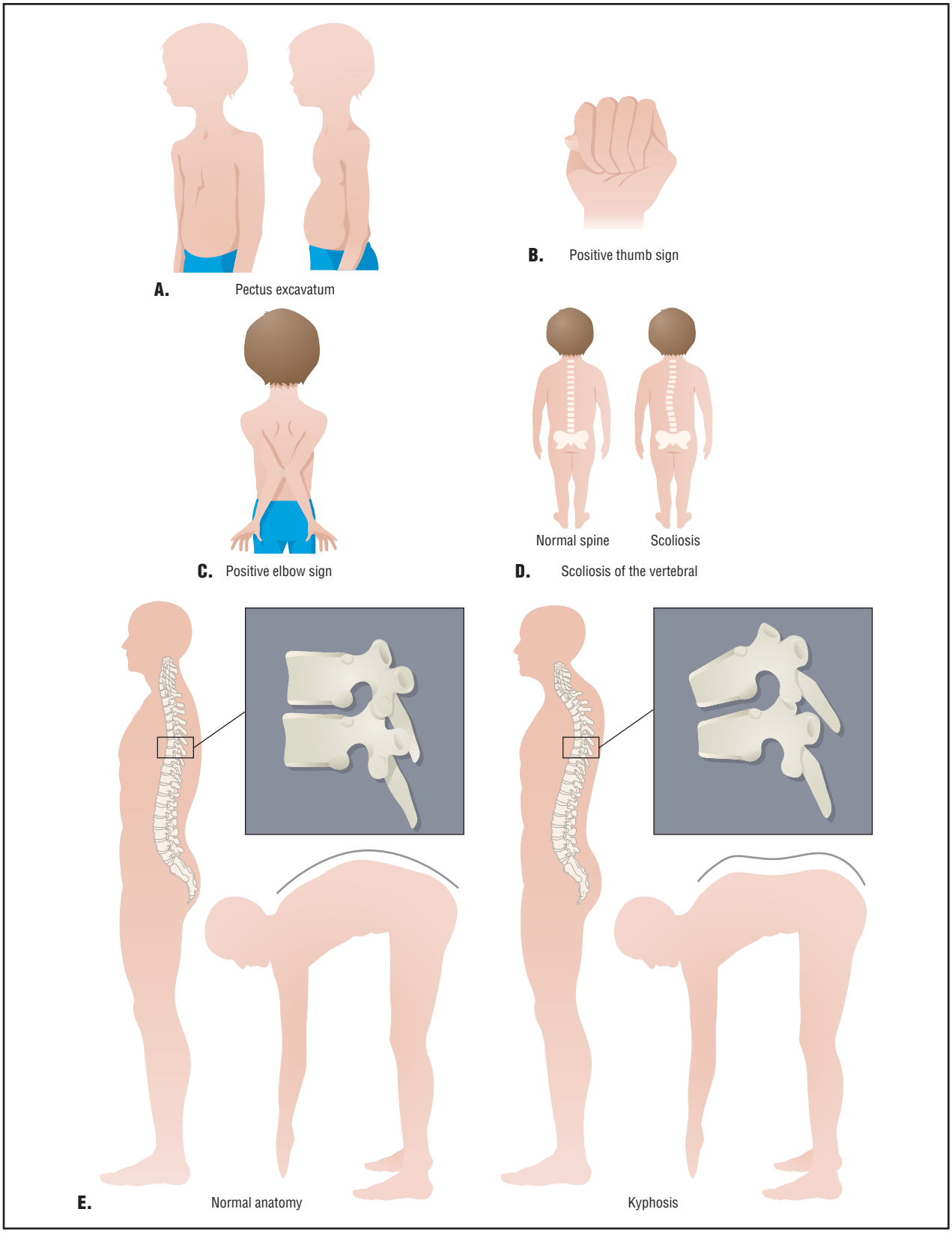
Disorders of the chest and lower body

- Pectus excavatum. Pectus excavatum is a malformation of the chest in which the patient's breastbone, or sternum, is sunken inward. It can cause difficulties in breathing, especially if the heart, spine, and lung have been affected by Marfan syndrome. It may also cause concerns about appearance.
- Pectus carinatum. In other patients with Marfan syndrome the sternum is pushed outward and narrowed. Although pectus carinatum does not cause breathing difficulties, it can cause embarassment about appearance. A few patients may have a pectus excavatum on one side of their chest and a pectus carinatum on the other.
- Foot disorders. Patients with Marfan syndrome are more likely to develop pes planus (flat feet) or so-called "claw" or "hammer" toes than people in the general population. They are also more likely to have chronic pain in their feet.
- Protrusio acetabulae. The acetabulum is the socket of the hip joint. In patient's with Marfan syndrome, the acetabulum becomes deeper than normal during growth for reasons that are not yet understood. Although protrusio acetabulae does not cause problems during childhood and adolescence, it can lead to a painful form of arthritis in adult life.

Disorders of the eyes and face

Although the visual problems related to Marfan syndrome are rarely life-threatening, they are important in that they may be the patient's first indication of the disorder. Eye disorders related to the syndrome include the following:

- Myopia (nearsightedness). Most patients with Marfan develop nearsightedness, usually in childhood.
- Ectopia lentis. Ectopia lentis is the medical term for dislocation of the lens of the eye. Between 65% and 75% of patients with Marfan have dislocated lenses. This condition is an important indication for diagnosis of the syndrome because there are relatively few other disorders that produce it.
- **Glaucoma**. This condition is much more prevalent in patients with Marfan syndrome than in the general population.



Five common clinical signs for Marfan syndrome. Pectus excavatum (A) refers to the inward curve of the chest. Positive thumb sign (B) is the apperance of the thumb tip when making a closed fist. Positive elbow sign (C) is the ability to touch one's elbows behind their back. Scoliosis (D) is a marked side-to-side curvature of the spine, and kyphosis (E) is the hunchback form resulting from an outward curvature of the spine.

- Cataracts. Patients with Marfan syndrome are more likely to develop cataracts, and to develop them much earlier in life, sometimes as early as 40 years of age.
- Retinal detachment. Patients with Marfan syndrome are more vulnerable to this disorder because of the weakness of their connective tissues. Untreated retinal detachment can cause blindness. The danger of retinal detachment is an important reason for patients to avoid contact sports or other activities that could cause a blow on the head or being knocked to the ground.
- Other facial problems. Patients with Marfan sometimes develop dental problems related to crowding of the teeth caused by a high-arched palate and a narrow jaw.

Other disorders

- Striae. Striae are stretch marks in the skin caused by rapid weight gain or growth; they frequently occur in pregnant women, for example. Patients with Marfan often develop striae over the shoulders, hips, and lower back at an early age because of rapid bone growth. Although the patient may be self-conscious about the striae, they are not a danger to health.
- Obstructive sleep apnea. Obstructive sleep apnea refers to partial obstruction of the airway during sleep, causing irregular breathing and sometimes snoring. In patients with Marfan syndrome, obstructive sleep apnea is caused by the unusual flexibility of the tissues lining the patient's airway. This disturbed breathing pattern increases the risk of aortic dissection.

Diagnosis

Presently, there is no objective diagnostic test for Marfan syndrome, in part because the disorder does not produce any measurable biochemical changes in the patient's blood or body fluids, or cellular changes that could be detected from a tissue sample. Although researchers in molecular biology are currently investigating the FBNI gene through a process called mutational analysis, it is presently not useful as a diagnostic test because there is evidence that there can be mutations in the fibrillin gene that do not produce Marfan syndrome. Similarly, there is no reliable prenatal test, although some physicians have used ultrasound to try to determine the length of fetal limbs in at-risk pregnancies.

The diagnosis is made by taking a family history and a thorough examination of the patient's eyes, heart, and bone structure. The examination should include an echocardiogram taken by a cardiologist, a slit-lamp eye examination by an ophthalmologist, and a work-up of the patient's spinal column by an orthopedic specialist. In terms of the cardiac examination, a standard electrocardiogram (EKG) is not sufficient for diagnosis; only the echocardiogram can detect possible enlargement of the aorta. The importance of the slit-lamp examination is that it allows the doctor to detect a dislocated lens, which is a significant indication of the syndrome.

The symptoms of Marfan syndrome in some patients resemble the symptoms of **homocystinuria**, which is an inherited disorder marked by extremely high levels of homocystine in the patient's blood and urine. This possibility can be excluded by a urine test.

In other cases, the diagnosis remains uncertain because of the mildness of the patient's symptoms, the absence of a family history of the syndrome, and other variables. These borderline conditions are sometimes referred to as marfanoid syndromes.

Treatment and management

The treatment and management of Marfan syndrome is tailored to the specific symptoms of each patient. Some patients find that the syndrome has little impact on their overall lifestyle; others have found their lives centered on the disorder.

Cardiovascular system

After a person has been diagnosed with Marfan syndrome, he or she should be monitored with an echocardiogram every six months until it is clear that the aorta is not growing larger. After that, the patient should have an echocardiogram once a year. If the echocardiogram does not allow the physician to visualize all portions of the aorta, CT (computed tomography) or MRI (magnetic resonance imaging) may be used. In cases involving a possible aortic dissection, the patient may be given a TEE (transesophageal echocardiogram).

MEDICATIONS. A patient may be given drugs called beta-blockers to slow down the rate of aortic enlargement and decrease the risk of dissection by lowering the blood pressure and decreasing the forcefulness of the heartbeat. The most commonly used beta-blockers in patients with Marfan are propranolol (Inderal) and atenolol (Tenormin). Patients who are allergic to beta-blockers may be given a calcium blocker such as verapamil.

Because patients with Marfan syndrome are at increased risk for infective endocarditis, they must take a prophylactic dose of an antibiotic before having dental work or minor surgery, as these procedures may allow bacteria to enter the bloodstream. Penicillin and amoxicillin are the antibiotics most often used.

SURGICAL TREATMENT. Surgery may be necessary if the width of the patient's aorta increases rapidly or reaches a critical size (about 2 in, 5 cm). As of 2000, the most common surgical treatment involves replacing the patient's aortic valve and several inches of the aorta itself with a composite graft, which is a prosthetic heart valve sewn into one end of a Dacron tube. This surgery has been performed widely since about 1985; most patients who have had a composite graft have not needed additional surgery.

Patients who have had a valve replaced must take an anticoagulant medication, usually warfarin (Coumadin), in order to minimize the possibility of a clot forming on the prosthetic valve.

Musculoskeletal system

Children diagnosed with Marfan syndrome should be checked for scoliosis by their pediatricians at each annual physical examination. The doctor simply asks the child to bend forward while the back is examined for changes in the curvature. In addition, the child's spine should be x rayed in order to measure the extent of scoliosis or kyphosis. The curve is measured in degrees by the angle between the vertebrae as seen on the x ray. Curves of 20° or less are not likely to become worse. Curves between 20° and 40° are likely to increase in children or adolescents. Curves of 40° or more are highly likely to worsen, even in an adult, because the spine is so badly imbalanced that the force of gravity will increase the curvature.

Scoliosis between 20° and 40° in children is usually treated with a back brace. The child must wear this appliance about 23 hours a day until growth is complete. If the spinal curvature increases to 40° or 50°, the patient may require surgery in order to prevent lung problems, back pain, and further deformity. Surgical treatment of scoliosis involves straightening the spine with metal rods and fusing the vertebrae in the straightened position.

Spondylolisthesis is treated with a brace in mild cases. If the slippage is more than 30°, the slipped vertebra may require surgical realignment.

Dural ectasia can be distinguished from other causes of back pain on an MRI. Mild cases are usually not treated. Medication or spinal shunting to remove some of the spinal fluid are used to treat severe cases.

Pectus excavatum and pectus carinatum can be treated by surgery. In pectus excavatum, the deformed breastbone and ribs are raised and straightened by a metal bar. After four to six months, the bar is removed in an outpatient procedure.

Protrusio acetabulae may require surgery in adult life to provide the patient with an artificial hip joint, if the arthritic pains are severe.

Pain in the feet or limbs is usually treated with a mild analgesic such as acetaminophen. Patients with Marfan syndrome should consider wearing shoes with low heels, special cushions, or orthotic inserts. Foot surgery is rarely necessary.

Visual and dental concerns

Patients with Marfan syndrome should have a thorough eye examination, including a slit-lamp examination, to test for dislocation of the lens as well as nearsightedness. Dislocation can be treated by a combination of special glasses and daily use of 1% atropine sulfate ophthalmic drops, or by surgery.

Because patients with Marfan syndrome are at increased risk of glaucoma, they should have the fluid pressure inside the eye measured every year as part of an eye examination. Glaucoma can be treated with medications or with surgery.

Cataracts are treated with increasing success by implant surgery. It is important, however, to seek treatment at medical centers with eye surgeons familiar with the possible complications of cataract surgery in patients with Marfan syndrome.

All persons with Marfan syndrome should be taught to recognize the signs of retinal detachment (sudden blurring of vision in one eye becoming progressively worse without pain or redness) and to seek professional help immediately.

Children with Marfan should be evaluated by their dentist at each checkup for crowding of the teeth and possible misalignment, and referred to an orthodontist if necessary.

People with Marfan syndrome should avoid sports or occupations that require heavy weight lifting, rough physical contact, or rapid changes in atmospheric pressure (e.g., scuba diving). Weight lifting increases blood pressure, which in turn may enlarge the aorta. Rough physical contact may cause retinal detachment. Sudden changes in air pressure may produce pneumothorax. Regular noncompetitive physical exercise, however, is beneficial for patients. Good choices include brisk walking, shooting baskets, and slow-paced tennis.

Social and lifestyle issues

Smoking is particularly harmful for patients with Marfan because it increases their risk of emphysema.

Until very recently, women with Marfan syndrome were advised to avoid pregnancy because of the risk of

aortic enlargement or dissection. The development of beta-blockers and echocardiograms, however, allows doctors now to monitor patients throughout pregnancy. It is recommended that patients have an echocardiogram during each of the three trimesters of pregnancy. Normal, vaginal delivery is not necessarily more stressful than a Caesarian section, but patients in prolonged labor may have a Caesarian birth to reduce strain on the heart. A pregnant woman with Marfan syndrome should also receive **genetic counseling** regarding the 50% risk of having a child with the syndrome.

Children and adolescents with Marfan syndrome may benefit from supportive counseling regarding appearance, particularly if their symptoms are severe and causing them to withdraw from social activities. In addition, families may wish to seek counseling regarding the effects of the syndrome on relationships within the family. Many people respond with guilt, fear, or blame when a genetic disorder is diagnosed in the family, or they may overprotect the affected member. Support groups are often good sources of information about Marfan syndrome; they can offer helpful suggestions about living with it as well as emotional support.

Prognosis

The prognosis for patient's with Marfan syndrome has improved markedly in recent years. As of 1995, the life expectancy of people with the syndrome had increased to 72 years; up from 48 years in 1972. This dramatic improvement is attributed to new surgical techniques, improved diagnosis, and new techniques of medical treatment.

The most important single factor in improving the patient's prognosis is early diagnosis. The earlier that a patient can benefit from the new techniques and lifestyle modifications, the more likely he or she is to have a longer life expectancy.

Resources

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Silverman, D., et al. "Life expectancy in the Marfan syndrome." *American Journal of Cardiology* 75 (1995): 157–60.

ORGANIZATION

Alliance of Genetic Support Groups, 4301 Connecticut Avenue, Washington, DC, 20008. (202). 652-5553. <http:www.geneticalliance.org>.

National Marfan Foundation, 382 Main Street, Port Washington, NY, 11050. (516). 883-8712. <http:www.marfan.org>.

Rebecca J. Frey, PhD

Marie-Strumpell spondylitis bechterew syndrome *see* Ankylosing spondylitis

Maroteaux-Lamy syndrome (MPS VI) *see* Mucopolysaccharidosis (MPS)

Marshall syndrome

Definition

Marshall syndrome is a very rare genetic disorder with an autosomal dominant pattern that equally affects males and females. It is caused by an abnormality in collagen, which is a key part of connective tissue.

Description

Marshall syndrome was first described by Dr. D. Marshall in 1958 and it has been studied periodically by researchers since then. The disease is most apparent in the facial features of those affected, which include an upturned nose, eyes spaced widely apart, making them appear larger than normal, and a flat nasal bridge. This facial formation gives subjects a childlike appearance. The upper part of the skull is unusually thick, and deposits of calcium may appear in the cranium. Patients may also have palate abnormalities. In addition, they may experience early **osteoarthritis**, particularly in the knees.

Myopia (nearsightedness), cataracts, and **glaucoma** are common in Marshall syndrome. Moderate to severe hearing loss is often preceded by many incidents of otitis media (middle ear infection) and can occur in children as young as age three. Some patients also have osteoarthritis, particularly of the knees.

In the years following Dr. Marshall's discovery, some physicians have argued that Marshall syndrome is actually a subset of **Stickler syndrome**, a more common genetic disorder. Individuals with both syndromes have similar facial features and symptoms. However, other experts have argued against this view, stating that Marshall syndrome is a distinct disorder on its own. For example, most patients with Stickler syndrome have cataracts, while this problem is less common among those with Marshall syndrome. In addition, most subjects with Marshall syndrome have moderate to severe hearing loss, which rarely occurs among those with Stickler syndrome, who have normal hearing.

Genetic research performed in 1998 and 1999 revealed that both sides were right. There are clear genetic differences between the two syndromes. There are also patients who have apparent overlaps of both syndromes.

In 1998, a study used **genetic testing** to establish that a collagen genetic mutation on COL11A1 caused Marshall syndrome and that a change on COL2A1 caused Stickler syndrome. It also found that other types of mutations could cause overlaps of both syndromes.

A study in 1999 described a genetic study of 30 patients from Europe and the United States, all of whom were suspected to have either Marshall or Stickler syndrome. These genetic findings confirmed those of the previous (1998) study. Twenty-three novel mutations of COL11A1 and COL2A1 were found among the subjects. Some patients had genetic overlaps of both Marshall and Stickler syndromes.

Physical differences were also noted between the two syndromes. For example, all the patients with Marshall syndrome had moderate to severe hearing loss, while none of the patients with Stickler syndrome had hearing loss. About half the patients with overlapping disorders of both diseases had hearing loss. All the patients with Marshall syndrome had short noses, compared to about 75% of the patients with Stickler syndrome. Palate abnormalities occur in all patients with Stickler syndrome, compared to only about 80% of those with Marshall syndrome. Also, about a third of the Stickler patients had dental abnormalities, compared to 11% of the patients with Marshall syndrome. Those with Stickler (71%) had a higher percentage of cataracts than those with Marshall syndrome (40%). Patients with Marshall syndrome were much more likely to have short stature than those with Stickler syndrome.

KEY TERMS

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Myopia—Nearsightedness. Difficulty seeing objects that are far away.

Osteoarthritis—A degenerative joint disease that causes pain and stiffness.

Saddle nose—A sunken nasal bridge.

Genetic profile

The **gene** name for Marshall syndrome is Collagen, Type XI, alpha 1. The gene symbol is COL11A1. The chromosomal location is 1p21. Marshall syndrome is an autosomal dominant genetic trait and the risk of an affected parent transmitting the gene to the child is 50%. Human traits are the product of the interaction of two genes from that condition, one received from the father and one from the mother. In dominant disorders, a single copy of the abnormal gene (received from either parent) dominates the normal gene and results in the appearance of the disease. The risk of transmitting the disorder from affected parent to offspring is 50% for each pregnancy regardless of the sex of the resulting child.

Demographics

Because of the rarity of this disease, very little demographic data is available. Less than 100 cases of individuals with this syndrome have been reported worldwide in medical literature. Some cases are probably undiagnosed because of the high expense of genetic testing. It is known that Marshall syndrome presents in infancy or early childhood and severe symptoms such as hearing loss and cataracts manifest before the age of 10 years. Adults with the syndrome retain the facial traits that are characteristic of this disease, such as flat nose, large nasal bridge and widely spaced eyes. Among those with

Stickler syndrome, in contrast, these distinctive facial characteristics diminish in adulthood.

Signs and symptoms

Characteristic features of this disease are short upturned nose with a flat nasal bridge. Some patients also have glaucoma, crossed eyes, detached retinas, and protruding upper teeth. Patients often have short stature compared to other family members without the disease.

Diagnosis

Individuals are diagnosed by their features as well as by the very early onset of serious eye and ear disease. Because Marshall syndrome is an autosomal dominant hereditary disease, physicians can also note the characteristic appearance of the biological parent of the child. Genetic testing is costly, thus, it is not ordered for most people. As a result, people may be diagnosed as possible Marshall syndrome or possible Stickler syndrome, based on their symptoms and appearance.

Treatment and management

Marshall syndrome cannot be cured; however, the symptoms caused by the disease should be treated. Children with Marshall syndrome should have annual eye and ear checkups because of the risk for cataracts and hearing loss. Cataract surgery will be needed if cataracts develop. At present, the only treatment for the progressive hearing loss is a hearing aid. The flat "saddle nose" can be altered with cosmetic surgery. If a child with Marshall syndrome has osteoarthritis, doctors may advise against contact sports.

Prognosis

As they age, vision and hearing problems will generally worsen for patients with Marshall syndrome. Many will also develop osteoarthritis at an earlier age than for patients without Marshall syndrome, such as in the teens or twenties. Because there are so few identified cases, it is unknown what the life expectancy is of afflicted individuals.

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Stickler Involved People. 15 Angelina, Augusta, KS 67010. (316) 775-2993. <http://www.sticklers.org/sip>.

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Christine Adamec

Marshall-Smith syndrome

Definition

Marshall-Smith syndrome is a childhood condition involving specific facial characteristics, bone maturation that is advanced for the individual's age, failure to grow and gain weight appropriate for the individual's age, and severe respiratory (breathing) problems.

Description

Marshall-Smith syndrome (MSS) was first described in two males seen in 1971 by Drs. Marshall, Graham, Scott, and Smith. They noticed changes in the skeletal system of these patients. Bones normally mature through several stages, naturally progressing through these stages with time. Specifically, a young child's bones have more cartilage and less calcium deposits than an adult's bones. A child's bones appear less "dense" on an x ray than an adult's bones. A constant feature of MSS is skeletal maturation that is advanced for age. For example, in 1993 a newborn child with MSS was found to have the "bone age" of a three year-old child.

Specific facial features in MSS include a wide and prominent forehead, protruding and widely spaced eyes, a very small chin, and a small, upturned nose. Because individuals may not gain weight or grow well, they are often smaller than other children of the same age. There are often problems with structures in the respiratory tract (such as the larynx and trachea) and this can lead to dif-

ficulty with breathing. Pneumonia, or a lung infection, is common because of this; these can occur several times.

Significant mental and physical delays are almost always expected in MSS. Since children with MSS are often hospitalized for long periods of time to help treat respiratory problems, they may also be slower to do physical things like crawling or walking.

No two patients with MSS have the exact same symptoms, as there is some variability with the condition. There are no alternate names for Marshall-Smith syndrome, though it is sometimes incorrectly referred to as **Weaver syndrome**, a separate condition with similar symptoms.

Families with MSS can be put under a great deal of stress, because long-term hospitalizations in the intensive care unit are common for children with MSS.

Genetic profile

The vast majority of people with MSS are unique in their family; there is usually no family history of the condition. Because of this, MSS is thought to be a random, sporadic event when it occurs. As of 2001, no specific **gene** has been associated with MSS, and other genetic background is still largely unknown. Standard **genetic testing**, such as chromosome analysis and metabolic studies, typically are normal for patients with MSS.

In 1999, a group in Saudi Arabia reported a young girl with features of MSS who had a chromosome abnormality. She was found to have some duplication of the material on a region of chromosome 2. This has led researchers to believe that the gene for MSS may actually be on chromosome 2. As of 2001, this is the only individual with MSS found to have a chromosome abnormality. Current research is under way to determine the exact genetic cause for MSS.

Demographics

Marshall-Smith syndrome is very rare in the general population. In fact, no statistical rates are available for the condition. It appears to be present across the world, affecting males and females equally.

Signs and symptoms

The most medically serious complication in MSS is the associated respiratory problems. Structures in the respiratory system, such as the larynx and trachea, may not function properly because they can be "floppy," soft, and less muscular than usual. Because of this, airways can become plugged or clogged, since air does not move through to clear them like usual. Mucus may start collecting, causing an increased amount of bacteria that can lead to pneumonia. Ear infections are common, because the bacteria can spread to the ears as well. Internal nasal passages may be narrower in people with MSS, which can also pose difficulty with breathing.

Children with MSS may have problems with eating, due to similar reasons that they may have difficulty breathing. Additionally, they may have a weak "suck" and "swallowing" reflex, normally controlled by muscular movements. As mentioned earlier, another feature of MSS is lack of proper growth and weight gain. This can be in part due to the difficulty in feeding for these individuals, though they are often very small even at birth.

Advanced bone age is present in all people with MSS. In particular, the bones of someone with MSS appear more dense on an x ray than they should, according to their age. While x rays of their hands and wrists often determine a person's "bone age," people with MSS often have a generalized advanced bone age within their

KEY TERMS

Cartilage—Supportive connective tissue which cushions bone at the joints or which connects muscle to bone.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Gastrostomy—The construction of an artificial opening from the stomach through the abdominal wall to permit the intake of food.

Hirsuitism—The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

Larynx—The voice box, or organ that contains the vocal cords.

Phalanges—Long bones of the fingers and toes, divided by cartilage around the knuckles.

Trachea—Long tube connecting from the larynx down into the lungs, responsible for passing air.

Tracheostomy—An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

Umbilical hernia—Protrusion of the bowels through the abdominal wall, underneath the navel.

entire skeleton. They may also have broad middle phalanges of the hand, which can be seen on an x ray.

Facial characteristics of people with MSS include those mentioned earlier, but other features may also occasionally be present. These can be blue-tinged sclerae (the white sections of the eyes), a large head circumference (measurement around the head), and a small, triangle-shaped face (with the point of the triangle being at the chin).

Occasionally, creases in the hands are "deeper" than usual in people with MSS. The first ("big") toe can also be longer and bigger than usual. Additional features include hirsuitism and an umbilical hernia. Hearing loss can sometimes occur. Ears may be larger, have a "crumpled" appearance, or be lower on the head than usual.

Changes in the brain can occur in MSS. An individual was reported in 1997 to have a smaller optic nerve (the nerve the connects the eyes to the brain) than usual, and had some vision problems as a result. Some children may be missing the corpus callosum, a structure in the brain. Mental and physical delays are commonly present in MSS, and are usually quite significant. These may in part be due to the brain abnormalities that are sometimes seen. There may be partial to complete lack of speech for individuals with MSS, another sign of the mental delays.

Diagnosis

Because there is no genetic testing available for Marshall-Smith syndrome, all individuals have been diagnosed through a careful physical examination and study of their medical history.

Advanced skeletal age can be seen on x rays of the patient's hands and wrists, since this is the typical way to assess bone age. A full x ray survey of the body is a good way to assess age of other bones as well. Advanced bone age is always seen in Marshall-Smith syndrome, but it may also be present in other genetic syndromes. **Sotos syndrome** involves similar skeletal findings, but individuals are generally larger than usual and can have mental delays. Weaver syndrome includes advanced skeletal maturation, but individuals are often larger than usual and have other specific facial characteristics (such as very narrow, small eyes). These and other conditions can be ruled out if the respiratory complications and facial characteristics seen in MSS are not present.

Treatment and management

As mentioned earlier, long hospitalizations are common for people with MSS. Most of these involve treating severe respiratory complications of MSS. These types of complications often necessitate placing a tracheotomy to assist with breathing. Manual removal of the mucus buildup by suctioning near the tracheotomy is common. Frequent pneumonia is common, and intravenous antibiotics are often the treatment, as in people without MSS. There is no specific treatment for the advanced bone age.

Because feeding can be difficult for children with MSS, a gastrostomy is often needed, and feeding is done directly through the gastrostomy tube. It is a challenge to make sure children with MSS maintain proper growth, and sometimes a gastrostomy is the only way to achieve this.

Prognosis

Marshall-Smith syndrome is considered a childhood condition because affected individuals do not typically survive past childhood. There is no long-term research on the disease due to it being rare and not typically present in adults.

Most children with MSS die in early infancy, often by three years of age, due to severe respiratory complications and infections that may result from them. There have been reports of children surviving until age seven or eight, but these children did not have severe respiratory problems. These children give hope that the condition is variable, and not every person diagnosed with the condition will have a severely shortened lifespan.

Resources

ORGANIZATIONS

Arc (a National Organization on Mental Retardation). 1010 Wayne Ave., Suite 650, Silver Spring, MD 20910. (800) 433-5255. Fax: (301) 565-5342, Info@thearc.org, <http://www.thearclink.org>.

Human Growth Foundation. 997 Glen Cove Ave., Glen Head, NY 11545. (800) 451-6434 or (516) 671-4041. Fax: (516) 671-4055. hgfound@erols.com. <http://www. hgf1 @hgfound.org>.

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408, Phone: (806) 737-8186 or (888) LPA-2001. Fax: (806) 797-8830, lpadatabase@juno.com, <http://www.lpaonline.org>.

Little People's Research Fund, Inc. 80 Sister Pierre Dr., Towson, MD 21204-7534. (800) 232-5773 or (410) 494-0055, Fax: (410) 494-0062. <http://pixelscapes.com/lprf>.

MAGIC Foundation for Children's Growth. 1327 N. Harlem Ave., Oak Park, IL 60302. (800) 362-4423 or (708) 383-0808. Fax: (708) 383-0899. mary@magicfoundation.org. <http://www.magicfoundation.org>.

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Deepti Babu, MS

Martin-Bell syndrome *see* **Fragile X syndrome**

MASA syndrome *see* **X-linked hydrocephaly**

MCAD deficiency

Definition

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is a rare genetic disorder characterized by a deficiency of the MCAD enzyme. This enzyme is responsible for the breakdown of certain fatty acids into chemical forms that are useable by the human body. MCAD deficiency accounts for approximately one to three of every 100 cases of sudden infant death syndrome (SIDS). MCAD deficiency is transmitted through a non-sex linked (autosomal) recessive trait. The first recognized cases of MCAD deficiency were reported in 1982.

Description

Medium chain acyl-CoA dehydrogenase (MCAD) is one of four enzymes in the mitochondria of the cells that is responsible for the breakdown of medium chain fatty acids into acetyl-CoA. Medium chain fatty acids are defined as fatty acids containing between four and 14 carbon atoms. Acetyl-CoA, the desired product of the breakdown of these fatty acids, is a two-carbon molecule. MCAD is the enzyme responsible for the breakdown of straight-chain fatty acids with four to 14 carbons. There are two other enzymes that are responsible for the breakdown of short straight-chain chain (less than four carbon) fatty acids, and long straight-chain (more than 14 carbon) fatty acids. These other two enzymes are not able to take over the function of MCAD when MCAD is deficient.

Individuals affected with MCAD deficiency produce a form of the MCAD enzyme that is not nearly as efficient as the normal form of MCAD. This lack of efficiency results in a greatly diminished, but still functional, capability to break down medium chain fatty acids.

Genetic profile

The **gene** that is responsible for the production of MCAD is located on chromosome 1 at 1p31. Twenty-six different mutations of this gene have been identified as causing MCAD deficiency; however, 95–98% of all cases are the result of a single point mutation. In this mutation, an adenosine is substituted for a guanine in base 985 (G985A), which causes a substitution of lysine (AAA) by glutamic acid (GAA) in residue 329 of the MCAD protein.

MCAD deficiency is a recessive disorder. This means that in order for a person to be affected with MCAD deficiency, he or she must carry two abnormal copies of the MCAD gene. In a population of individuals known to be affected with the G985A mutation, 81% were found to be homozygous for this mutation (two **chromosomes**, each with the same mutation). The remaining 19% were found to be heterozygous for the G985A mutation (only one chromosome carried the G985A mutation), but their other chromosomes carried one of the other MCAD gene mutations.

Demographics

MCAD deficiency is estimated to occur in approximately one out of every 13,000 to 20,000 live births. This estimate is confounded to a certain degree by the fact that

KEY TERMS

Apnea—An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

Carnitine—An amino acid necessary for metabolism of the long-chain fatty acid portion of lipids. Also called vitamin B_7.

Enzyme efficiency—The rate at which an enzyme can perform the chemical transformation it is expected to accomplish. This is also called turnover rate.

Founder effect—Increased frequency of a gene mutation in a population that was founded by a small ancestral group of people, at least one of whom was a carrier of the gene mutation.

Hepatomegaly—An abnormally large liver.

Hyperammonemia—An excess of ammonia in the blood.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Medium chain acyl-CoA dehydrogenase—Abbreviated MCAD, this is the enzyme responsible for the breakdown of medium chain fatty acids in humans. People affected with MCAD deficiency produce a form of MCAD that is not as efficient as the normal form of MCAD.

Medium chain fatty acids—Fatty acids containing between four and 14 carbon atoms.

up to 25% of all individuals affected with MCAD deficiency die the first time they exhibit any symptoms of the disease. Many of these children are often misdiagnosed with either sudden infant death syndrome (SIDS) or Reye syndrome. Unless an autopsy is performed, MCAD generally goes undetected in these individuals; and, even then, unless the physician performing the autopsy is familiar with MCAD deficiency, the cause of death may still be misreported.

MCAD deficiency is seen almost exclusively in Caucasians of Northern European descent (this includes people from every European country not bordering the Mediterranean Sea). Approximately 80% of the Caucasian population of the United States can be considered a part of this subpopulation. In this subpopulation, it is estimated that one in every 40 to 100 people is a carrier of the G985A mutation, and one in every 6,500 to 20,000 people is homozygous in this mutation. Homozygous individuals (carriers of two sets of the G985A mutation) should be affected with MCAD deficiency; however, the incidence rate of MCAD deficiency is lower than that predicted from the carrier populations. There are two possible reasons for the lower number of observed cases of MCAD deficiency than the carrier data suggests should occur. First, many individuals with MCAD deficiency may be misdiagnosed. Secondly, there may be a significant number of homozygous people who for unknown reasons remain unaffected (asymptomatic).

As a comparison, one in every 29 Caucasians is a carrier for **cystic fibrosis**, but only one in every 3,300 people in this subpopulation develop the disease.

The high frequency of a single mutation leading to MCAD deficiency, combined with the extreme similarity of the other known mutations to this mutation, and the high concentration of MCAD deficiency within a single subpopulation, suggests a founder effect from a single person in a Germanic tribe.

Because MCAD deficiency is a recessive disease, both parents must be carriers of this trait in order for their children to be affected. If both parents carry a copy of the mutated gene, there is a 25% likelihood that their child will be homozygous for MCAD deficiency. Genetically, the probability that an affected person will have a sibling who is also affected is also 25%. In population studies of known MCAD deficient individuals, it has been observed that an average of 32% of these individuals have at least one sibling either known to be affected with MCAD deficiency or to have died with a misdiagnosis of SIDS.

Signs and symptoms

There is no classic set of symptoms that characterize MCAD deficiency. The severity of symptoms observed in individuals affected with MCAD deficiency ranges from no symptoms at all (asymptomatic) to the occurrence of death upon the first onset of symptoms. The first symptoms of MCAD deficiency generally occur within the first three years of life. The average age of onset of the first symptoms is one year of age. Some individuals become symptomatic prior to birth. The onset of symptoms in adults is extremely rare.

Lethargy and persistent vomiting are the most typical symptoms of MCAD deficiency. The first episode of symptoms is generally preceded by a 12 to 16 hour period of stress. Most affected individuals show intermittent periods of low blood sugar (hypoglycemia) and higher than normal amounts of ammonia in the blood (hyperammonemia). An abnormally large liver (hepatomegaly) is also associated with MCAD deficiency.

Approximately half of all individuals showing symptoms of MCAD deficiency for the first time experience respiratory arrest, cardiac arrest, and/or sudden infant death. Between 20% and 25% of all MCAD deficiency affected infants die during their first episodes of symptoms.

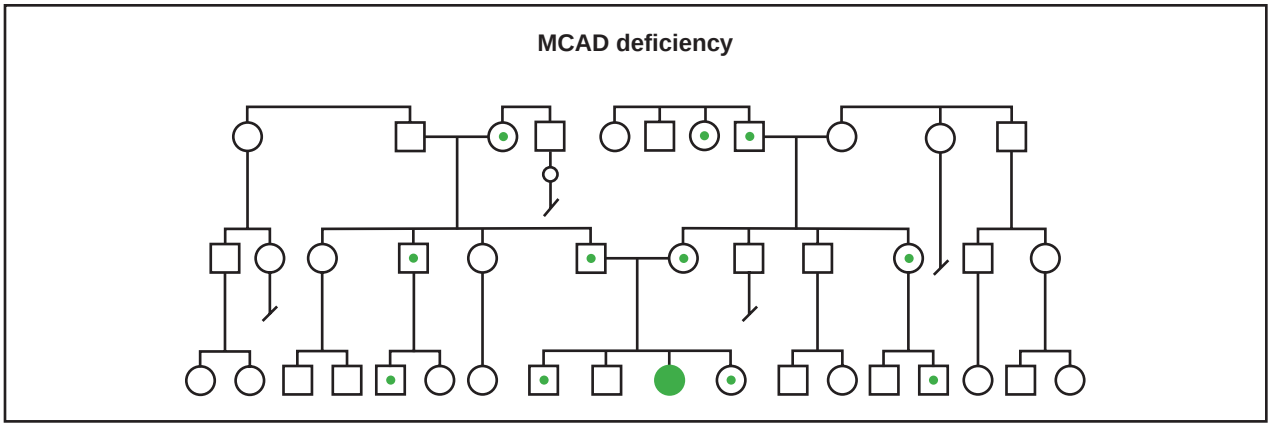
Some individuals affected with MCAD deficiency also are affected with a degenerative disease of the brain and central nervous system (encephalopathy). Seizures, coma, and periods of halted breathing (apnea) have also been seen in people with MCAD deficiencies.

Long-term symptoms of MCAD deficiency may include: attention deficit disorder (ADD), **cerebral palsy**, mental retardation, and/or developmental delays.

The severity of the symptoms associated this MCAD deficiency is linked to the age of the person when the symptoms first happen. The risk of dying from an onset of the disease is slightly higher in individuals who show the first symptoms after the age of one year. The highest risk ages are the ages of 15 to 26 months. Seizures and encephalopathy are most frequently seen in affected individuals between the ages of 12 and 18 months. Seizures at these ages are often associated with future death during a symptomatic episode, recurrent seizures throughout life, the development of cerebral palsy, and/or the development of speech disabilities.

Diagnosis

The Departments of Health in Massachusetts and North Carolina require mandatory newborn screening for MCAD deficiency. California has a voluntary newborn screening policy. Additionally, Neo Gen Screening offers voluntary newborn screening at birthing centers throughout the Northeastern United States. In September 2000, Iowa also began a pilot program to screen all newborns in



(Gale Group)

that state. It is expected that MCAD deficiency screening will become mandatory statewide in Iowa sometime in 2001.

These newborn screening methods employ either a recently developed (1999) tandem mass spectrometry (MS/MS) blood test method or a PCR/FRET analysis. The MS/MS test discovers the presence of the G985A mutation in the MCAD gene by the difference in molecular weight in this gene versus the molecular weight of the normal MCAD gene.

In the PCR/FRET test, a sample of blood is drawn and the **DNA** is extracted. This DNA is then reproduced multiple times by the polymerase chain reaction (PCR amplification). Once enough sample has been made, the sample is labeled with a fluorescent chemical that binds specifically to the region of chromosome 1 that contains the MCAD gene. How this fluorescent chemical binds to the MCAD gene region containing the G985A mutation allows the identification of homozygous G985A, heterozygous G985A, and normal (no G985A mutations) MCAD genes (FRET analysis).

An older method for the detection of MCAD deficiency is a urine test that checks for elevated levels of the chemicals hexanoylglycine and phenylpropionylglycine.

Prenatal testing for MCAD deficiency is also available using a test similar to the PCR/FRET blood test. In this case, however, the DNA to be studied is extracted from the amniotic fluid rather than from blood. Another prenatal test involves studying the ability of cultured amniotic cells to breakdown added octanoate, an 8-carbon molecule that requires MCAD to break it down.

Because MCAD deficiency is generally treatable if it is recognized prior to the onset of symptoms, most parents of a potentially affected child choose to wait until birth to have their children tested.

Treatment and management

Because individuals affected with MCAD deficiency can still break down short chain and long chain fatty acids at a normal rate and most have a diminished, but functional, ability to break down medium chain fatty acids, a precipitating condition must be present in order for symptoms of MCAD deficiency to develop. The most common precipitators of MCAD deficiency symptoms are stress caused by fasting or by infection. At these times, the body requires a higher than normal breakdown of medium chain fatty acids. MCAD deficient individuals often cannot meet these increased metabolic demands.

The main treatments for MCAD deficiency are designed to control or avoid precipitating factors. Persons affected with MCAD deficiency should never fast for more than 10 to 12 hours and they should strictly adhere to a low-fat diet. Blood sugar monitoring should be undertaken to control episodes of hypoglycemia. During acute episodes, it is usually necessary to administer glucose and supplement the diet with carbohydrates and high calorie supplements.

Many individuals affected with MCAD deficiency benefit from daily doses of vitamin B7 (L-carnitine). This vitamin is responsible for transporting long chain fatty acids across the inner mitchondrial membrane. Elevated levels of L-carnitine ensure that these individuals breakdown long chain fatty acids in preference to medium chain fatty acids, which helps prevent acute symptomatic episodes of MCAD deficiency. Additionally, L-carnitine helps remove toxic wastes from the bloodstream to the urine, so it is also pivotal in controlling hyperammonemia.

Some individuals affected with MCAD deficiency present symptoms for the first time when they receive the diphtheria-pertussis-tetanus (DTP) vaccine. It is impor-

tant that any person suspected to be affected with MCAD deficiency receive treatment for hypoglycemia in connection with the administration of this vaccine. Chicken pox and middle ear infections (otitis media) have also been shown to initiate symptoms of MCAD deficiency.

Prognosis

MCAD deficiency has a mortality rate of 20–25% during the first episode of symptoms. If an affected individual survives this first attack, the prognosis is excellent for this individual to have a normal quality of life as long as appropriate medical treatment is sought and followed.

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ORGANIZATIONS

Fatty Oxidation Disorders (FOD) Family Support Group. 805 Montrose Dr., Greensboro, NC 24710. (336) 547-8682. fodgroup@aol.com. <http://www.fodsupport.org/welcome.htm>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Organic Acidemia Association. 13210 35th Ave. North, Plymouth, MN 55441. (763) 559-1797. Fax: (863) 694-0017. <http://www.oaanews.org>.

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Paul A. Johnson

McCune-Albright syndrome

Definition

A disorder characterized by abnormalities in bone development, skin pigmentation, and endocrine gland function.

Description

The McCune-Albright syndrome is an uncommon disorder in which a mutation distributed across various cell populations results in a wide variety of clinical features. The most notable features are abnormal bone development, pigmented skin spots, and endocrine gland dysfunction.

Genetic profile

Scientists have identified a specific genetic defect that causes McCune-Albright syndrome. The defect is a mutation in the *GNAS1* **gene**, which is associated with a type of G protein. These proteins are present in a wide variety of cells in the body. G proteins are part of the system of proteins and enzymes that regulate communication between cells and various agents such as hormones and the nervous system. If a cell's G protein is abnormal, this sets off a chain reaction that causes the cell to multiply inappropriately and the subsequent cells produce too much hormone. The mutation first occurs in a single cell during the early stages of formation of the embryo. This cell multiplies into many other cells that eventually become part of the bones, skin, and endocrine glands. The severity of the syndrome is dependent on the percentage of cells involved. The earlier the mutation occurs, the more cells are affected. There is some evidence that a second mutation must occur before the clinical manifestations become evident.

The McCune-Albright syndrome is not hereditary.

Demographics

This syndrome is uncommon. As of 1996, there were only 158 cases reported in scientific papers. Of course, this figure probably underestimates the true prevalence of the syndrome, since only patients with typical or severe clinical features were likely to be reported. The female to male ratio is approximately two to one.

Signs and symptoms

The McCune-Albright syndrome is classically characterized by the three main features described below.

Abnormal bone development

Pockets of abnormal fibrous tissue develop within the bone, which may cause deformity, fractures, and nerve entrapment. Most of these lesions appear during the first decade of life. The pelvis and femur, or thigh bone, are the most commonly involved areas of the skeleton. Bony abnormalities in the skull can cause blindness or deafness. The majority of patients with McCune-Albright syndrome have many of these lesions, hence the name *polyostotic fibrous dysplasia.*

In addition to these fibrous lesions, some patients develop osteosarcoma, which is a malignant tumor of the bone. Although it has not been proven, these tumors may originate from the fibrous lesions within the bone.

Pigmented skin spots

Patients with McCune-Albright syndrome typically have pigmented skin lesions called *café au lait* spots. These are flat areas of discoloration of the skin that may be associated with a variety of conditions. Those that are found in McCune-Albright syndrome have irregular borders. They are located on one side of the body, usually on the buttocks or lower back. Sometimes these lesions are present at birth.

Endocrine gland dysfunction

The McCune-Albright syndrome is striking for its association with a number of endocrine abnormalities. Endocrine glands are those that secrete hormones directly into the blood stream to be transported to other tissues of the body. In McCune-Albright syndrome, one or more of these glands secrete abnormally high amounts of hormone.

The most common endocrine abnormality in McCune-Albright syndrome is excessive function of the gonads, which are ovaries in females and testicles in males. The ovaries secrete estrogen and the testicles secrete testosterone. When these organs secrete too much estrogen or testosterone in children, the result is early puberty. Females are more commonly affected than males. In fact, early puberty in a girl is the hallmark sign of McCune-Albright syndrome. Typically, these girls will develop secondary sexual characteristics, such as breasts and pubic hair, before the age of nine. Menses also begins early. Sometimes the normal sequence of development is disrupted, in that affected girls might have menses before breast or pubic hair development.

Hyperfunction of the pituitary gland also occurs in McCune-Albright syndrome, resulting in excess production of growth hormone and/or prolactin. Excess growth hormone leads to **acromegaly**, or marked overgrowth of certain bones and tissues, especially in the face and extremities. Some people with acromegaly grow to very tall stature. Acromegaly in McCune-Albright syndrome affects boys and girls equally. If too much prolactin is produced, then breast tissue will secrete milk inappropriately, both in boys and girls. This is called galactorrhea. In some patients, the pituitary gland dysfunction is caused by a tumor.

Other endocrine glands that may be hyperactive are the thyroid and adrenal glands. The thyroid gland produces thyroid hormones, which help regulate the body's metabolism. If excess thyroid hormones are produced, i.e. hyperthyroidism, then patients may have diarrhea, weight loss, nervousness, tremor, and rapid heartbeat. In some patients, the hyperthyroidism is caused by thyroid nodules. The adrenal gland produces several hormones in the steroid hormone class, such as cortisol, aldosterone, and testosterone. Cortisol is most commonly over-produced. Similar to the pituitary gland, hyperfunction of the adrenal gland in McCune-Albright syndrome is sometimes caused by tumors.

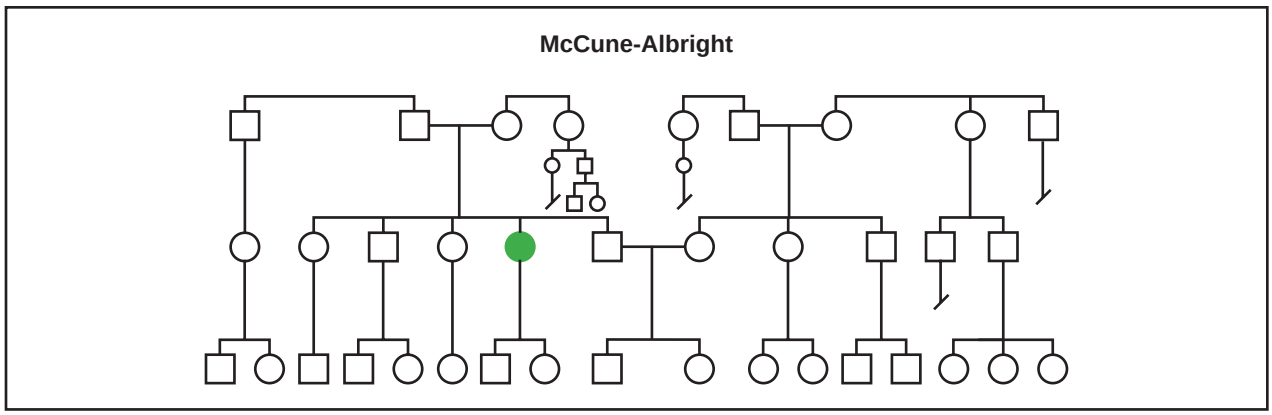
Another feature of McCune-Albright syndrome is phosphate deficiency caused by excess excretion of phosphate in the urine. Since phosphate is a vital mineral for bone formation, this results in soft bones and some degree of pain. This condition is called rickets in children and osteomalacia in adults. There are two theories that have been proposed to explain the loss of phosphate in the urine. First of all, it is thought that the fibrous bone lesions may produce an agent that circulates through the blood stream to the kidneys that makes the kidneys unable to retain phosphate. Secondly, perhaps the kidneys are intrinsically unable to retain the appropriate amount of phosphate.

It is important to emphasize the variability of clinical features among patients with McCune-Albright syndrome. Not every patient has the three features of bony lesions, pigmented skin spots, and endocrine abnormalities. Each patient is affected differently. There are also rare subtypes of the syndrome in which patients have hepatitis, cardiac arrythmias, or intestinal polyps.

KEY TERMS

Dysplasia—The abnormal growth or development of a tissue or organ.

Pituitary gland—A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicl-stimulating hormone (FSH).



(Gale Group)

Diagnosis

There is no single test that is diagnostic for McCune-Albright syndrome. Certain clinical features can be easily observed, such as skin pigmentation and early puberty. The bony abnormalities can be confirmed by x ray. Blood tests for hormone levels can detect endocrine gland dysfunction.

Treatment and management

Likewise, there is no specific treatment that cures the disease. Testalactone, a drug that inhibits estrogen production, has been successful in the short term treatment of girls with early puberty, but long term treatment has not been very effective. Patients with pituitary tumors may benefit from drugs to reduce tumor size, or surgery to remove the tumors. Thyroid nodules can be treated by surgical removal or destruction with radioactive iodine. In addition, adrenal tumors can be removed by surgery.

Prognosis

The lifespan in patients with McCune-Albright syndrome is essentially normal. Women who experienced early puberty as girls are generally fertile.

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Kevin Osbert Hwang, MD

McKusick-Kaufman syndrome

Definition

The McKusick-Kaufman syndrome (MKS) is a developmental disorder characterized by a group of conditions that include congenital heart disease, buildup of fluid in the female reproductive tract and extra toes and fingers.

Description

McKusick reported the first case of a disorder which he called hydrometrocolpos syndrome in 1964. Shortly thereafter, Kaufman described another individual with a very similar group of abnormalities. Subsequent writers combined these syndromes into one, calling it the McKusick-Kaufman syndrome and characterizing its wide range of features.

MKS is the first human disorder to be attributed to a mutation occurring in a **gene** and affecting a type of molecule called a chaperonin. Chaperonins are sometimes called "protein cages" in that they protect cells by capturing and refolding misshapen proteins that could otherwise interfere with normal cellular functions.

Genetic profile

MKS is inherited in an autosomal recessive pattern, meaning that a child must inherit two altered genes, one from each parent, to be affected. An altered gene responsible for a rare developmental syndrome found predominantly among the Old Order Amish population has been identified. Mutations in the gene responsible for MKS have been identified on chromosome 20p12 in an Amish family. Scientists have isolated the McKusick-Kaufman syndrome gene by positional cloning.

Based on an earlier genetic analysis of the Old Order Amish population, a research group looked at a region of chromosome 20 thought to contain the gene responsible for the syndrome. A technique called sample sequencing was then used to find candidate genes in that region. One of those genes, dubbed MKS, was altered in a sample from an Amish person as well as in a sample from a non-Amish person diagnosed with MKS. In both people, errors or "misspellings" in the genetic code were found that would disturb the function of the MKS gene. It was observed that the chemical building blocks (amino acids) coded by the MKS gene appeared to be very similar to those that make up the chaperonins. Although the function of the protein made by the MKS gene is unclear as of 2001, it appears to be involved in the production of proteins associated with the development of limbs, the heart, and the reproductive system.

In 2000, researchers identified a **gene mutation** that causes **Bardet-Biedl syndrome** (BBS), a rare genetic disorder that is related to MKS. BBS is believed to be due to a complete absence of the gene responsible for MKS.

Demographics

Between one and three percent of the Amish people of Lancaster County, Pennsylvania are believed to be carriers of the disease, having just one copy of the altered gene. The related Bardet-Biedl syndrome is estimated to occur between one in 125,000 and one in 160,000 people. Among an isolated community in Newfoundland, Canada, the prevalence is estimated to be ten times higher.

Signs and symptoms

Many abnormalities associated with MKS are visible in a physical exam. They include the following abnormalities:

- Limbs: polydactyly (extra fingers or toes)
- Genitourinary system in females: hydrometrocolpos (accumulation of fluids in the uterus and vagina), transverse vaginal membrane, vaginal atresia (absence of a vagina)
- Genitourinary system in males: hypospadias (abnormal opening of the urinary tract), prominent scrotal raphe (ridges), micropenis, cryptorchidism (undescended testicles)
- Cardiac: **congenital heart defects**
- Head: pituitary **dysplasia** (abnormal development of the pituitary gland), choanal atresia (bony or membranous blockage of the passageway between the nose and pharynx), **retinitis pigmentosa** (overactive cells in the retina of the eye leading to blindness), tracheo-esophageal fistula (abnormal passage in the throat region)
- Skeleton: vertebral anomalies
- Abdomen: distension, peritoneal cysts, Hirschsprung megacolon (enlarged and poorly functioning large intestine)
- Other: nonimmune **hydrops fetalis** (massive build-up of fluids in a fetus or newborn)

KEY TERMS

Atresia—An abnormal condition in which a structure that should be hollow is fused shut.

Chaperonin—A molecule that captures and refolds misshapen proteins that might interfere with normal cellular functions; also called a protein cage.

Choanal atresia—A bony or membranous blockage of the passageway between the nose and pharynx at birth.

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Dysplasia—The abnormal growth or development of a tissue or organ.

Genome—A term used to describe a complete representation of all of the genes in a species.

Hydrometrocolpos—An abnormal accumulation of fluids in the uterus and vagina.

Hydrops fetalis—A condition characterized by massive edema in a fetus or newborn.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Polydactyly—The presence of extra fingers or toes.

Positional cloning—Cloning a gene simply on the basis of its position in the genome, without having any idea of the function of the gene.

Tracheo-esophageal fistula—Abnormal connection between the trachea and esophagus, frequently associated with the esophagus ending in a blind pouch.

Diagnosis

A diagnosis of McKusick-Kaufman syndrome is usually made at birth when a newborn is given a post-natal physical exam. The diagnosis is made by noting physical

McKusick-Kaufman syndrome has a high incidence amoung Amish families. *(Photo Researchers, Inc.)*

abnormalities such as: polydactyly, hydrometrocolpos, a transverse vaginal membrane, vaginal atresia, hypospadias, prominent scrotal raphe, micropenis, cryptorchidism, congenital heart defects, pituitary dysplasia, choanal atresia, tracheo-esophageal fistula, vertebral anomalies, abdominal distension, peritoneal cysts, Hirschsprung megacolon, or nonimmune hydrops fetalis. The probability of a correct diagnosis increases with each additional abnormality present. A diagnosis may sometimes be confirmed with a chromosomal analysis. Abnormal development of the pituitary gland (pituitary dysplasia) and vertebral abnormalities are visible in a CT or MRI scan. Peritoneal cysts are commonly diagnosed by ultrasonography.

Treatment and management

Treatment of MKS is limited to surgical correction of defects. Timing is often important. Many abnormalities, if uncorrected, can quickly become life threatening. For example, hydrops fetalis is often fatal. **Genetic counseling** before marriage is recommended for persons who are possible carriers of MKS. Affected rural and Amish girls should be delivered in settings that allow rapid surgical intervention and correction of abnormalities. Such actions could be life saving.

Prognosis

With appropriate genetic counseling and complete family histories, individuals born with MKS can receive prompt treatment. With rapid initial surgical intervention, most of these persons can live relatively normal lives. Some abnormalities, such as hypospadias, vaginal atresia, choanal atresia, tracheo-esophageal fistula, or Hirschsprung megacolon, may require multiple operations. Due to the risk of retinitis pigmentosa, vision should be monitored closely.

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Hypospadias Association of America. 4950 S. Yosemite Street, Box F2-156, Greenwood Village, CO 80111. hypospadiasassn @yahoo.com. <http://www.hypospadias.net>.

National Institutes of Health, Office of Rare Diseases. 31 Center Dr., Bldg. 31, Room 1B-19, MSC 2084, Bethesda, MD 20892-2084. (301) 402-4336. Fax: (301) 480-9655. hh70f@nih.gov. <http://rarediseases.info.nih.gov/ord>.

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L. Fleming Fallon. Jr., MD, PhD, DrPH

Meckel's diverticulum

Definition

Meckel's diverticulum is a congenital pouch (diverticulum) approximately two inches in length and located at the lower (distal) end of the small intestine. It was

named for Johann F. Meckel, a German anatomist who first described the structure.

Description

The diverticulum is most easily described as a blind pouch that is a remnant of the omphalomesenteric duct or yolk sac that nourished the early embryo. It contains all layers of the intestine and may have ectopic tissue present from either the pancreas or stomach.

The rule of twos is the classical description. It is located about 2 ft from the end of the small intestine, is often about 2 in in length, occurs in about 2% of the population, is twice as common in males as females, and can contain two types of ectopic tissue—stomach or pancreas. Many who have a Meckel's diverticulum never have trouble but those that do present in the first two decades of life and often in the first two years.

There are three major complications that may result from the development of Meckel's diverticulum. The most common problem is inflammation or infection that mimics appendicitis. This diagnosis is defined at the time of surgery for suspected appendicitis. Bleeding caused by ectopic stomach tissue that results in a bleeding ulcer is the second most frequent problem. Bleeding may be brisk or massive. The third potential complication is obstruction due to intussusception, or a twist around a persistent connection to the abdominal wall. This problem presents as a small bowel obstruction, however, the true cause is identified at the time of surgical exploration.

Genetic profile

Meckel's diverticulum is not hereditary. It is a vestigial remnant of the omphalomesenteric duct, an embryonic structure that becomes the intestine. As such, there is no genetic defect or abnormality.

Demographics

Meckel's diverticulum is a developmental abnormality that is present in about 2% of people, but does not always cause symptoms. Meckel's diverticula (plural of diverticulum) are found twice as frequently in men as in women. Complications occur three to five times more frequently in males.

Signs and symptoms

Symptoms usually occur in children under 10 years of age. There may be bleeding from the rectum, pain and vomiting, or simply tiredness and weakness from unnoticed blood loss. It is common for a Meckel's diverticulum to be mistaken for the much more common disease appendicitis. If there is obstruction, the abdomen will distend and there will be cramping pain and vomiting.

KEY TERMS

Appendectomy—The procedure to surgically remove an appendix.

Appendicitis—Inflammation of the appendix.

Appendix—A portion of intestine attached to the cecum.

Cecum—The first part of the large bowel.

Congenital—Refers to a disorder which is present at birth.

Distal—Away from the point of origin.

Ectopic—Tissue found in an abnormal location.

Intussusception—One piece of bowel inside another, causing obstruction.

Isotope—Any of two or more species of atoms of a chemical element with the same atomic number and nearly identical chemical behavior but with differing atomic mass and physical properties.

Peptic ulcer—A wound in the bowel that can be caused by stomach acid or a bacterium called *Helicobacter pylori.*

Volvulus—A twisted loop of bowel, causing obstruction.

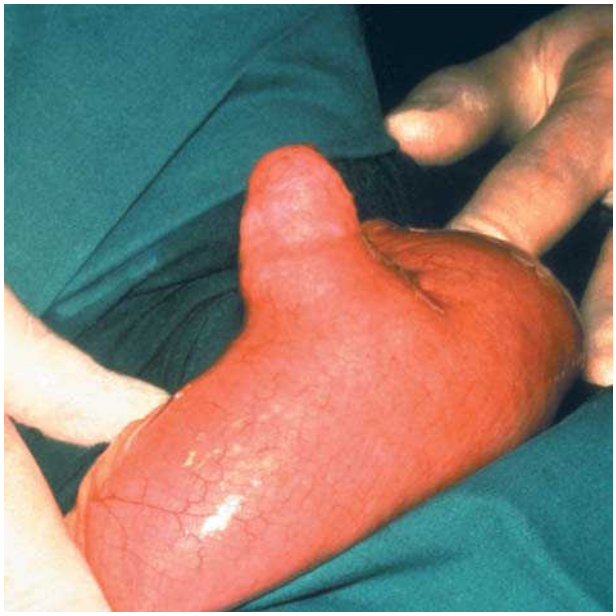
Diagnosis

The situation may be so acute that surgery is needed on an emergency basis. This is often the case with bowel obstruction. With heavy bleeding or severe pain, whatever the cause, surgery is required. The finer points of diagnosis can be accomplished when the abdomen is open for inspection during a surgical procedure. This situation is called an acute abdomen.

If there is more time (not an emergency situation), the best way to diagnose Meckel's diverticulum is with a nuclear scan. A radioactive isotope injected into the bloodstream will accumulate at sites of bleeding or in stomach tissue. If a piece of stomach tissue or a pool of blood shows up in the lower intestine, Meckel's diverticulum is indicated.

Treatment and management

A Meckel's diverticulum that is causing discomfort, bleeding, or obstruction must be surgically removed. This procedure is very similar to an appendectomy.



A patient with Meckel diverticulum. *(Custom Medical Stock Photo, Inc.)*

Prognosis

The outcome after surgery is usually excellent. The source of bleeding, pain, or obstruction is removed so the symptoms also disappear. A Meckel's diverticulum will not return.

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ORGANIZATIONS

American Academy of Family Physicians. 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672. (913) 906-6000. <http://www.aafp.org/>, fp@aafp.org.

American Academy of Pediatrics. 141 Northwest Point Boulevard, Elk Grove Village, IL 60007-1098. (847) 434-4000. Fax: (847) 434-8000. kidsdoc@aap.org. <http://www.aap.org/default.htm>.

American College of Gastroenterology. 4900 B South 31st Street, Arlington, VA 22206. (703) 820-7400. Fax: (703) 931-4520. <http://www.acg.gi.org>.

American College of Surgeons. 633 North St. Clair St., Chicago, IL 60611-32311. (312) 202-5000. Fax: (312) 202-5001. postmaster@facs.org. <http://www.facs.org/>.

American Medical Association. 515 N. State Street, Chicago, IL 60610. (312) 464-5000. <http://www.ama-assn.org/>.

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L. Fleming Fallon, Jr., MD, DrPH

Meckel syndrome *see* **Meckel-Gruber syndrome**

Meckel-Gruber syndrome

Definition

Meckel-Gruber syndrome (MGS) is an inherited condition that causes skull abnormality, enlarged cystic kidneys, liver damage, and extra fingers and toes. Findings vary between affected infants (even in the same family), as well as between ethnic groups. Infants with MGS are usually stillborn or die shortly after birth.

Description

The first reports of MGS were published in 1822 by Johann Friedrich Meckel. G.B. Gruber also published reports of MGS patients in 1934 and gave it the name dysencephalia splanchnocystica. MGS is also known as Meckel syndrome and Gruber syndrome.

MGS affects many different organ systems including the central nervous system (brain and spinal cord), face, kidneys, liver, fingers and toes, and occasionally the bones of the arms and legs. Some researchers believe that abnormal development and differentiation of the embryonic mesoderm (the early tissue layer that contributes to the formation of the bones, cartilage, muscles, reproductive system, blood cells, heart, and kidneys) is related to MGS. The cells of the mesoderm must divide, migrate, associate, and specialize in a precise manner to form these body parts. Any problem in any step of the process can lead to multiple abnormalities in various organ systems.

Since MGS causes severe birth defects and death in the newborn period, it can be devastating for families. Extensive examination and autopsy is often needed to confirm a diagnosis of MGS, delaying the family's answers regarding their child's death. Most parents do not know they are at risk until they have a child with MGS. This can cause feelings of anger, disbelief, and guilt.

Genetic profile

The autosomal recessive **inheritance** pattern in MGS is well-documented. MGS affects males and females equally. Parents of affected children are assumed to be carriers and have a 25% chance of MGS recurrence in each pregnancy. A healthy brother or sister of an affected child has a two-thirds chance of being an MGS carrier.

Research involving families in Finland (where MGS is more common) led to the first MGS **gene** being mapped (localized) to the short arm of chromosome 17. This means that the gene location has been narrowed down to a small potential area, but the exact location and precise details about the gene are still unknown. Non-Finnish families did not show evidence of a causative gene linked to chromosome 17. This led to the search for a second MGS gene. Studies of Northern African and Middle Eastern families resulted in the second MGS gene being mapped to the short arm of chromosome 11. More research is being performed to learn more about the precise location of both MGS genes, gene changes that cause MGS, and the role of the genes in early development.

KEY TERMS

Bile duct—A passageway that carries bile (fluid secreted by the liver involved in fat absorption) from the liver to the gallbladder to the small intestine.

Clubfoot—Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

Trimester—A three-month period. Human pregnancies are normally divided into three trimesters: first (conception to week 12), second (week 13 to week 24), and third (week 25 until delivery).

Demographics

MGS has an estimated incidence between one in 13,000 births and one in 140,000 births. This means that between one person per 50 and one person per 180 is an MGS carrier. The incidence varies among ethnic groups. Several ethnic populations have an increased incidence of MGS. The incidence in Finland is one in 9,000 births (one person in 50 is a carrier). The incidence is also higher among Belgians and Bedouins in Kuwait with one affected birth in 3,500 (one person in 30 is a carrier). The highest incidence is reported in the Gujarati Indians with one affected birth per 1,300 (one person in 18 is a carrier). The incidence among Jews in Israel is one in 50,000 (one person in 112 is a carrier). Cases of MGS have been reported in North America, Europe, Israel, Indonesia, India, Kuwait, and Japan.

Signs and symptoms

The three hallmark features of MGS are **encephalocele**, polycystic kidneys, and polydactyly. Approximately 90% of infants with MGS have an encephalocele. This is an opening in the skull that allows brain tissue to grow outside of the skull. Virtually 100% of infants with MGS have enlarged kidneys with cysts. Polydactyly (extra fingers and/or toes) is present in about 80% of affected children. The polydactyly is usually postaxial (the extra fingers/toes are on the same side of the hand/foot as the smallest finger/toe). In MGS, the polydactyly usually affects both the hands and feet. There may also be webbing of the fingers and toes—the skin between the fingers or toes fails to separate—leaving the digits attached to each other.

Internal examination of babies with MGS also revealed that virtually 100% have liver abnormalities. This can include halted development of the bile ducts,

extra bile ducts, enlarged bile ducts, and loss of blood vessels. The liver is also usually enlarged. These liver changes are now considered by most to be another hallmark feature of MGS.

Babies with MGS often have similar facial features. Some reported features are eyes that are closer together or farther apart than usual, broad and flat nose, broad cheeks, and a wide mouth with full lips. Other features are commonly seen in MGS and are thought to be caused by a low amount of amniotic fluid surrounding the baby before birth. These features are sloping forehead, small jaw, low-set ears, and short, webbed neck. Low fluid prior to birth also frequently causes **clubfoot** in the newborn.

Other common features of MGS are abnormalities of the genitalia and cleft palate. The external (visible) genitalia are often small or ambiguous (not clearly male or female). There have also been reports of babies with MGS having both male and female reproductive parts (hermaphrodite). Cleft palate is seen in about 45% of babies with MGS. Cleft lip is less common but has been reported.

The symptoms of MGS are variable. Not all infants with MGS show the same signs and the characteristic signs range in severity. Some features have been described in some babies with MGS but are not as common. These include heart defects, enlarged spleen, extra spleen, hydrocephaly (extra water in the brain), absence or underdevelopment of other brain structures, and arm and leg bones that are shortened, thickened, and bowed.

Diagnosis

Some of the features of MGS can be detected on prenatal ultrasound early in the second trimester. At that time, an encephalocele can often be seen as well as other brain abnormalities. Enlarged kidneys can also be detected at this time. As the pregnancy continues, a low amount of amniotic fluid becomes apparent. Enlarged kidneys make the abdomen appear and measure larger than usual. Cysts will make the kidneys appear bright or white on an ultrasound instead of the usual gray color.

Measurement of the alpha-fetoprotein (AFP) level from either maternal blood or amniotic fluid may help to detect an encephalocele (although most encephaloceles are closed and do not elevate AFP levels). AFP can be measured in amniotic fluid after about 12 weeks of pregnancy and in maternal blood after about 15 weeks of pregnancy. AFP elevation in either test increases the chance of an encephalocele or other abnormality in the baby's skull or spine.

When signs of MGS are seen on prenatal ultrasound in the absence of a family history, MGS is often suspected but not confirmed until after birth and autopsy. A chromosome test can be performed before birth to rule out chromosome abnormalities such as trisomy 13. However, autopsy is usually needed to distinguish MGS from other syndromes with similar features. Every organ system of the baby is carefully examined for abnormal development.

Families at risk for recurrence of MGS can combine early ultrasound with either maternal blood AFP or amniotic fluid AFP for early detection. If early ultrasound reveals no signs of MGS, later scans are still recommended because of the variability in expression and severity. No routine genetic tests are currently available to these families.

Treatment and management

There is no effective treatment or cure for MGS. Babies with MGS have extensive birth defects that require many surgeries to repair. Encephaloceles can be repaired by surgery after birth. Surgeries are most successful for infants with small skull abnormalities. Encephaloceles put infants at high risk for infection. The abnormalities seen in the kidneys and liver often leave the organs nonfunctional. There is often no way to repair the organs other than transplant. Even if all of these problems could be solved, infants with MGS often have underdeveloped lungs that cannot support life after birth. The lungs are underdeveloped because of the low amount of amniotic fluid prior to birth. Due to the extensive birth defects, the extensive surgeries needed to correct them, and the poor prognosis, babies born with MGS are given minimum care for comfort and warmth.

When MGS is suspected in an unborn baby, parents should be given information about the range of symptoms of MGS and the poor prognosis. Parents should also be cautioned that a diagnosis of MGS often cannot be confirmed until after birth. Prognosis can vary if the baby has atypical signs of MGS or if the baby has a different syndrome. Elective termination of affected pregnancies may be an option for some couples.

Prognosis

The prognosis for MGS is quite poor. Many infants with MGS are stillborn. Those that are born living usually die shortly after birth in the first hours, days, or weeks of life. Death is usually due to inability to breathe (underdeveloped lungs), infection (opening in the skull), or organ failure (decreased function of kidneys and liver). MGS is variable and there have been a couple reports of

infants with milder symptoms living longer. One infant with MGS lived until four months of age. Another lived to seven months of age after surgical repair of a small encephalocele. At birth he had cystic kidneys but normal kidney function. These two case reports show that longer survival is rare but possible because of the variable expression of MGS.

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Amie Stanley, MS

Mediterranean anemia *see* **Beta-thalassemia**

Medium-chain acyl-coenzyme A *see* **MCAD deficiency**

Melnick-Fraser syndrome *see* **Branchiootorenal syndrome**

Menkes syndrome

Definition

Menkes syndrome is a sex-linked recessive condition characterized by seizures and neurological deterioration, abnormalities of connective tissue, and coarse, kinky hair. Affected males are often diagnosed within the first few months of life and die in early childhood.

Description

Menkes syndrome is also known as Menkes disease and "kinky hair syndrome." It was originally described in 1962 based on a family of English and Irish descent who had five male infants with a distinctive syndrome of progressive neurological degeneration, peculiar hair, and failure to thrive. Each of the boys appeared normal at birth but, by the age of several months, developed seizures and began to regress in their physical skills. Each child died at an early age, with the oldest surviving only until three-and-a-half years. In 1972, Menkes syndrome was linked to an inborn copper deficiency. It is now clear that this lack of copper, an essential element for normal growth and development, inhibits the work of specific enzymes in the body. The clinical signs and symptoms of Menkes syndrome are a direct result of these biochemical abnormalities.

Approximately 90–95% of patients with Menkes syndrome have a severe clinical course. This represents classical Menkes syndrome. Males with milder forms of Menkes syndrome have also been described. The mildest presentation is now known as occipital horn syndrome (OHS), which is allelic to Menkes syndrome: both conditions are due to different mutations in the same **gene**. Mutations responsible for OHS primarily cause connective tissue abnormalities and have significantly milder effects on intellectual development. Individuals with OHS also live longer than those with classical Menkes syndrome.

Genetic profile

Menkes syndrome is an X-linked recessive condition. The gene, which was identified in 1992, is located on the long arm of the X chromosome at band 13.3 (Xq13.3). It is extremely unusual for a female (with two X **chromosomes** in her cells) to be affected, although it has been reported. Males, who have only one X chromosome, make up the overwhelming majority of patients.

Approximately one-third of affected males are due to a new mutation in the mother's egg cell. There is usually a negative family history, or no other affected male family members. When the mutation occurs as an isolated, random change, the mother's risk of having another affected son is low.

On the other hand, the remaining two-thirds of affected males are born to carrier mothers. Often, there is a family history of one or more affected male relatives (e.g., uncle, brother, cousin), all of whom are related to one another through the maternal side. Carrier females are normal but face a risk of passing on the gene for Menkes syndrome to their children. A carrier mother has a 25% risk of having an affected son, 25% risk of having an unaffected carrier daughter, 25% risk of having a normal son, and a 25% risk of having a normal, non-carrier daughter. These risks apply to each pregnancy.

The Menkes syndrome gene, also known as MNK or ATP7A, is a large gene known to encode a copper-transporting protein. Individuals with Menkes syndrome have low levels of copper in their blood. Their cells are able to take in copper but the metal is unable to leave the cell and be delivered to crucial enzymes that require copper in order to function normally. As a result, copper accumulates in the body tissues, and clinical abnormalities occur. Most symptoms of Menkes syndrome, such as skeletal changes and abnormal hair, may be explained by the loss

of specific enzymes. However, the reasons for the brain degeneration are still not entirely clear.

A variety of mutations that cause Menkes syndrome have been identified in the MNK gene. Unfortunately, almost every family studied has had a unique mutation. This makes **genetic testing** difficult, particularly if the mutation in the family has not yet been determined. OHS is also due to mutations in the MNK gene.

Demographics

Menkes syndrome is relatively rare, with an estimated incidence of one in 100,000–250,000 male births. To put this into a different perspective, among the 3.5 million infants born annually in the United States, approximately 15–35 males would have Menkes syndrome.

Signs and symptoms

Infants with classical Menkes syndrome appear normal at birth and continue to develop normally for roughly the first eight to ten weeks of life. At approximately two to three months of age, affected infants begin to lose previously attained developmental milestones, such as head control and a social smile. They lose muscle tone and become hypotonic, or floppy, develop seizures, and begin to fail to thrive. Changes in the appearance of their face and hair become more apparent. A diagnosis of Menkes syndrome is often made around this time.

The clinical features of Menkes syndrome include:

Neurologic

- Mental deterioration and handicap due to structural and functional brain abnormalities
- Seizures
- Inability to regulate body temperature (hypothermia)
- Feeding and sleeping difficulties

Connective tissue

- Decreased muscle tone
- Tortuous blood vessels due to abnormal formation of blood vessel walls
- Abnormalities of bone formation, as noted by x ray (skull, long bones, and ribs)
- Bladder diverticulae
- Loose skin, particularly at the nape of neck, under the arms, and on the trunk
- Loose joints

Other

- Unusual facial features (jowly, pudgy cheeks, large ears)
- Abnormal hair, including the eyelashes and eyebrows
- Light, even for family, skin and hair coloring (hypopigmentation)
- Delayed eruption of teeth
- Impaired vision
- Normal hearing

The hair of individuals with Menkes syndrome deserves special discussion, particularly since this condition is sometimes also called kinky hair syndrome. Abnormal hair is not typically evident during the first few months of life. However, around the time that the other physical signs of the disorder become more apparent, the hair takes on an unusual appearance and texture. On magnified inspection, it is short, sparse, coarse, and twisted. It has been likened to the texture of a steel wool cleaning pad. It shows an unusual orientation, referred to as *pili torti*, a 180 degree twist of the hair shaft. It is usually fragile and breaks easily. The hair of all affected individuals shows these characteristic changes; it is likewise present in some women who are known gene carriers.

Death occurs early in males with Menkes syndrome, often by the age of three years in classical disease. However, longer survival is not unusual and is most likely due to more recent improvements in medical care. Severity of disease and its rate of progression are fairly consistent among untreated males in a single family.

Diagnosis

An initial diagnosis of Menkes syndrome is usually suspected based on the combination of physical features. However, as these features are generally subtle in the newborn period, they may be missed, particularly if there is no prior family history of the condition.

A somewhat common prenatal and newborn history has been recognized among affected infants. The histories often include: premature labor and delivery; large bruises on the infant's head after an apparently normal, uncomplicated vaginal birth; hypothermia; low blood sugar (hypoglycemia); and jaundice. Hernias may be present at either the umbilicus or in the groin area. These findings are non-specific and occur in normal pregnancies and unaffected infants. However, their presence may alert a knowledgeable physician that Menkes syndrome should be considered as a possibility, especially when other clinical signs are also present.

A clinical diagnosis is strongly supported by decreased serum levels of copper and ceruloplasmin, a protein in the blood to which the majority of copper is attached. Abnormal results, however, do not confirm the diagnosis since both copper and ceruloplasmin levels may also be low in normal infants during the first few months of life. A definitive diagnosis of Menkes syndrome is possible by either specific biochemical analysis to measure the level of copper accumulation in the cells or by identification of the responsible mutation in the MNK gene. Both types of analysis represent highly specialized testing and are available only through a limited number of laboratories in the world.

Prenatal diagnosis, in the context of a family history of the disorder, is possible. Ideally, a woman's carrier status will have been determined prior to a pregnancy as carrier detection may be difficult and time-consuming. Mutation analysis is the most direct and accurate way to determine carrier status. In order for this to be possible, the MNK mutation in an affected family member must have been previously determined. Linkage analysis is another possibility but requires blood samples from other family members, including the affected relative, to facilitate interpretation of results. If the affected relative is deceased, a stored **DNA** sample may be used.

Other, non-molecular methods of carrier detection include analysis of hair samples to look for areas of pili torti, increased fragility, or hypopigmentation. Skin cells cultured in the laboratory may be used to measure the accumulation of radioactive copper. However, these approaches are not always reliable, even in known carriers.

If a woman is found to be a non-carrier, prenatal testing for Menkes syndrome is generally not necessary in any of her pregnancies. However, in the event that a woman is a confirmed carrier, prenatal testing such as chorionic villus sampling (CVS) or **amniocentesis** may be offered. Ultrasound examinations alone will not assist in making a diagnosis. CVS or amniocentesis will determine the fetal sex: if female, additional testing is usually not recommended since carrier daughters would be expected to be normal. Carrier testing on the daughter may be performed after birth, if desired, or postponed until later in life.

Further testing is offered when a fetus is male. If mutation studies cannot be performed because the mutation in the family is unknown, biochemical analysis may be attempted. Biochemical testing has serious drawbacks, and a correct diagnosis may not always be possible. Tissue obtained during CVS normally has a very low copper content and is also very susceptible to contamination by maternal tissue or by outside sources, such as laboratory instruments or containers. As a result, if the copper level exceeds a certain level, an unaffected pregnancy could potentially be falsely identified as affected. Specific handling precautions are necessary to minimize this risk.

Similar concerns exist for a sample obtained by amniocentesis. Ordinarily, the cells obtained from this procedure are cultured and grown in the laboratory. A measurement is taken of the total amount of accumulated copper over a certain period. The timing of amniocentesis in the pregnancy is critical because the amniotic fluid cells do not grow as rapidly after a gestational age of 18 weeks. Problems in cell growth cause significant difficulties in the interpretation of the biochemical results.

Other methods of diagnosis are being investigated. Two that hold some promise are assessment of the concentration of copper in a sample of the placenta (extremely high in affected pregnancies) and the level of catecholamines (low) in a sample of blood from the umbilical cord. Both methods, which are fast, reliable, and performed immediately after delivery, clearly require a high level of suspicion of the disorder. In most cases, this will be based on a history of a previous affected son, abnormal or unclear prenatal testing results, or both.

KEY TERMS

Catecholamines—Biologically active compounds involved in the regulation of the nervous and cardiovascular systems, rate of metabolism, body temperature, and smooth muscle.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Diverticulae—Sacs or pouches in the walls of a canal or organ. They do not normally occur, but may be acquired or present from birth. Plural form of diverticula.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Linkage analysis—A method of finding mutations based on their proximity to previously identified genetic landmarks.

Tortuous—Having many twists or turns.

Women who do not have a family history of Menkes syndrome and are therefore not expected to be at-risk, are not offered this testing.

Treatment and management

The underlying, critical problem for patients with Menkes syndrome is an induced copper deficiency. Copper uptake is normal but the gene abnormality prevents the release of copper to the appropriate enzymes in the cells. Copper accumulates in the intestinal system, and patients are unable to meet their most basic nutritional needs. The most serious effects are apparent during the first year of life when growth of the brain and physical development are occurring most rapidly. Copper is required in order for both of these processes to occur normally.

Treatment of Menkes syndrome has focused on providing patients with an extra source of copper to try to deliver it to the enzymes that need it for normal function. Studies at the National Institutes of Health (NIH) have focused on the use of a copper-histidine compound in affected males. Copper-histidine is normally present in human serum and is most likely the form in which copper is absorbed by the liver. Also, in the laboratory, the presence of histidine in serum has been shown to increase the uptake of copper. Daily injections are the most successful form of treatment to date.

Two conclusions have been drawn from this work: (1) Treatment is more successful when started at an early age. Most, but not all, treated boys have achieved more normal developmental milestones and have had milder mental impairment. (2) Treatment is much less effective if started after the age of several months, or when neurologic symptoms have already begun. While milder improvements in the areas of physical development, personality, and sleeping habits have been reported in boys whose treatment started later, the degree of mental handicap has not been significantly altered.

A separate study in 1998 lent further support to these results. This study followed four affected males with classical Menkes syndrome, all of whom were started on copper-histidine treatment soon after birth. Three of the four males were born into families with other affected relatives; the fourth child was diagnosed at the age of three weeks. All four showed significant improvements in their development and clinical course. None were completely normal but their remaining clinical abnormalities were similar to those seen in patients with occipital horn syndrome. The oldest survivor of the group was 20 years old at the time of this publishing.

This information strongly supports the importance of nutritional therapy in the care of patients with Menkes syndrome. Early treatment is best but requires early diagnosis. It should also not be seen as a "cure." It has been shown to lessen the severity of the syndrome but not eliminate it. Thus, prenatal diagnosis, and its possible limitations, should continue to be discussed with prospective parents known to be at risk. Mutation studies should be performed, whenever possible, to increase the accuracy of testing results.

Prognosis

Death often occurs by the age of three years in untreated males with classical Menkes syndrome, although longer-term survivors have been reported. Treatment with supplemental copper has resulted in improved physical development, milder mental handicap, and extended lifespan in some affected males. However, not all patients have responded to the same extent. Additionally, patients treated after the onset of symptoms have done worse than those treated before symptoms occur. Research is continuing to refine the best dosage of copper-histidine, determine the optimal timing and route of treatment, and develop newer treatment strategies.

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Terri A. Knutel, MS, CGC

Mental retardation *see* **Smith-Fineman-Myers syndrome**

Mental retardation X-linked, syndrome 3 (MRXS3) *see* **Sutherland Haan X-linked mental retardation syndrome**

Mermaid syndrome *see* **Sirenomelia**

Metaphyseal dysplasia

Definition

Metaphyseal **dysplasia** is a very rare disorder in which the outer part of the shafts of long bones is unusually thin with a tendency to fracture. Aside from valgus knee deformities (commonly known as knock-knee), many patients with metaphyseal dysplasia exhibit few or no symptoms. However, the disorder comes in a variety of forms, some of which cause serious problems including mental retardation, blindness, and deafness.

Description

Metaphyseal dysplasia is frequently mistaken for craniometaphyseal dysplasia, a disorder characterized by the thickening of the bones of the head. Metaphyseal dysplasia is genetically distinct from craniometaphyseal dysplasia and has only mild effects on the skull. In fact, metaphyseal dysplasia is so subtle, often it cannot be detected by clinical observation and is uncovered only when x rays are taken for another purpose. The signs are immediately visible on x rays, however, particularly the cone-like flaring that occurs on the tubular bones of the leg. This flaring is similar in shape to the Erlenmeyer glass flasks used in laboratories.

Another name for metaphyseal dysplasia is Pyle's disease, after Edwin Pyle (1891-1961), an orthopedic surgeon in Waterbury, CT who first described it in 1931.

There are eight varieties of metaphyseal dysplasia. They are classified as: Jansen type, Schmid type, McKusick type, metaphyseal anadysplasia, Shwachman Diamond metaphyseal dysplasia, adenosine deaminase deficiency, Spahr type metaphyseal chondrodysplasia, and metaphyseal acroscyphodysplasia.

Genetic profile

Inheritance of metaphyseal dysplasia is autosomal recessive, meaning that both parents are carriers of an abnormal **gene** when a child exhibits symptoms. Children inheriting the gene from one parent become carriers. When both parents are carriers, each child has a 25% chance of having the disorder and a 50% chance of being a carrier. In the case of Jansen-type metaphyseal dysplasia, the chromosomal gene locus is 3p22-p21.1. In Schmid type metaphyseal dysplasia, the locus is 6q21-q22.3. For McKusick type (cartilage-hair hypoplasia), it is 9p13. In adenosine deaminase deficiency, the locus is 20q-13.11. The modes of inheritance for Jansen type, Schmid type, and adenosine deaminase deficiency are all autosomal dominant, meaning that a child may inherit the disorder if just one parent is a carrier. For all other varieties of metaphyseal dysplasia the modes are autosomal recessive, with the possible exception of metaphyseal anadysplasia, which may be X-linked recessive. In that case, whenever one parent is a carrier of the disorder, each child would have a chance of either inheriting it or being a carrier.

Demographics

This disorder is very rare, and the number of recorded cases is too small to draw firm demographic conclusions. There appears to be no preference based on sex.

Signs and symptoms

The characteristic sign of metaphyseal dysplasia is splaying of the long bones, more severely than in craniometaphyseal dysplasia. Gross Erlenmeyer flask flaring is seen in the tubular bones of the leg, particularly in the femur. Unlike craniometaphyseal dysplasia, few signs occur in the skull in metaphyseal dysplasia, apart from protrusions over the eye sockets.

Metaphyseal dysplasia is also marked by expanded bones of the rib cage and pelvis, and by changes in the angle of the lower jaw. The humerus bone of the arm tends to be unusually broad. Other signs include **scoliosis** (a sideways curvature of the spine) and **osteoporosis** (a condition that makes bones brittle). Patients may complain of muscle weakness or joint pain. Dentists may notice malocclusion, an inability of the teeth to properly close. Some spinal changes are possible, associated with the flaring of tubular bones. These may include platyspondyly, a broadening of the vertebrae.

KEY TERMS

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Dysplasia—The abnormal growth or development of a tissue or organ.

Splay—Turned outward or spread apart.

Jansen type

In addition to the above-mentioned signs, Jansen-type metaphyseal chondrodysplasia is characterized by short arms, legs, and stature (short-limbed dwarfism), which become apparent during early childhood. Affected children experience a gradual stiffening and swelling of their joints. Often, they develop a characteristic "waddling gait" and a stance that appears as if they were squatting. Some facial abnormalities may be evident at birth. These include prominent, widely spaced eyes, a receding chin, or a highly arched palate. Some affected adults develop unusually hardened bones in the back of the head, which sometimes results in deafness and/or blindness. Abnormal cartilage development may harden into rounded bone masses that may be noticeable on the hands, feet, and elsewhere. Other signs and symptoms associated with Jansen-type metaphyseal chondrodysplasia include clubbed fingers, a fifth finger permanently fixed in a bent position, fractured ribs, mental retardation, psychomotor retardation, and high blood levels of calcium. Curvature of the spine in these patients may be front-to-back as well as sideways. Testing the blood and urine for calcium can assist in confirming a diagnosis. Jansen-type metaphyseal chondrodysplasia was formerly referred to as metaphyseal dysostosis.

Schmid type

Like Jansen-type metaphyseal chondrodysplasia, Schmid type metaphyseal chondrodysplasia is also characterized by short-limbed dwarfism. Other special features may include an outward "flaring" of the lower rib cage, bowed legs, leg pain, a normal spine, and a hip deformity that causes the thigh bone to angle toward the body's center. Schmid type metaphyseal chondrodysplasia was first discovered in 1943 in a family of Mormons that had experienced 40 cases of the disorder over four generations. The first affected ancestor was traced back to 1833.

McKusick type

Like Jansen type and Schmid type, McKusick type metaphyseal chondrodysplasia is marked by short-limb dwarfism. Other features include thin, light-colored hair, loose-jointed fingers, elbows that cannot be fully extended, **Hirschsprung disease** (a birth defect in which the usual nerve network fails to develop around the rectum, and in some cases, the colon), and abnormalities of the immune system. In the shin, the tibia bone is uncharacteristically shorter than the fibula. Patients are at increased risk of developing cancers, especially of the skin and the lymph nodes. McKusick type metaphyseal chondrodysplasia is also known as cartilage hair hypoplasia syndrome. The disorder was first recognized in 1965 among the Old Order Amish. Billy Barty (1924-2000), the actor who founded the dwarfism advocacy group Little People of America, had McKusick type metaphyseal chondrodysplasia.

Metaphyseal anadysplasia

First noticed in 1971, metaphyseal anadysplasia is a form of metaphyseal dysplasia that starts early. Instead of appearing after puberty, some signs were found to be present at birth, but disappeared after two years. For example, parts of the long bones were irregular. In the thigh bones of these patients, there was an unusually low level of red blood cell production.

Shwachman-Diamond syndrome

In addition to the skeletal system, Shwachman-Diamond syndrome also affects the pancreas. It is characterized by inadequate absorption of fats because of abnormal pancreatic development and bone marrow dysfunction. Other unusual symptoms and signs include short stature, liver abnormalities, and low levels of any or all blood cells. Reduced levels of white blood cells may cause these patients to be vulnerable to repeated bouts with pneumonia, otitis media, and other bacterial infections. Shwachman-Diamond syndrome is also referred to as Shwachman-Bodian syndrome, Shwachman-Diamond-Oski syndrome, Shwachman syndrome, and congenital lipomatosis of the pancreas. Some researchers call it pancreatic insufficiency and bone marrow dysfunction.

Adenosine deaminase deficiency

A deficiency of Adenosine deaminase (ADA), an essential, broadly distributed enzyme, causes severe combined immunodeficiency disease. This can bring about a wide range of effects, including **asthma**, pneumonia, sinusitis, diarrhea, problems with the liver, kidneys, spleen and skeletal system, and failure to thrive. ADA deficiency is similar to McKusick type metaphyseal

chondrodysplasia in that both disorders include skeletal changes and problems with cellular immunity. ADA deficiency earned a special place in genetics history in 1990, when, in the first application of **gene therapy** in humans, it was corrected using genetically engineered blood.

Spahr type metaphyseal chondrodysplasia

This is one of several disorders that used to be called metaphyseal dysostosis. It is extremely rare, and its features include severely bowed legs and short-statured dwarfism. In some cases, the bowing of the knees is so severe as to require surgical correction. Spahr type is very similar to Schmid type metaphyseal chondrodysplasia, except that inheritance is believed to be autosomal recessive in Spahr type, unlike Schmid type, which is autosomal dominant.

Metaphyseal acroscyphodysplasia

This variety is also referred to as wedge-shaped epiphyses of the knees. Its special features include severely retarded growth, psychomotor retardation, abnormally small arms and legs, extremely short fingers, and curvature of the knees.

Diagnosis

Diagnosis is usually by x ray, in which the bone deformities of metaphyseal dysplasia are very noticeable, even if not apparent in a normal clinical examination. A medical doctor will look for valgus knee deformities. A radiologist will look for Erlenmeyer-flask shaped femur bones and ensure that any deformities to cranial bones are minor, to rule out craniometaphyseal dysplasia. The radiologist will also watch for abnormally broad humerus, radius, and ulna bones.

Treatment and management

Metaphyseal dysplasia cannot be directly treated, but some individual symptoms, such as osteoporosis or joint problems, may be treated or surgically corrected.

Prognosis

In many cases, patients with metaphyseal dysplasia may be symptomless and very healthy. Other patients, including those with Jansen-type metaphyseal chondrodysplasia, may have more severe complications including blindness, deafness, or mental retardation.

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David L. Helwig

Methylmalonic acidemia

Definition

Methylmalonic acidemia (MMA) is a group of disorders characterized by the accumulation of methylmalonic acid in the fluids of the affected individual. The first recognized cases of these disorders were described in 1967. All known genetic forms of MMA are non-sex linked (autosomal) and recessive. Some non-genetic cases have been reported in which the affected individuals were vegetarians who had been on prolonged cobalamin (vitamin B_{12}) deficient diets.

Description

Methylmalonic acidemia (MMA) is characterized by an accumulation of methylmalonic acid in the blood stream, which leads to an abnormally low pH (high acidity) in nearly every cell in the body (metabolic acidosis). A higher than normal accumulation of ketones in the blood stream (ketosis) similar to that seen in instances of **diabetes mellitus** is also associated with MMA. If left untreated, metabolic acidosis is often fatal.

Methylmalonic acid is an intermediate in the metabolism of fats and proteins. This chemical accumulates in the bodies of individuals affected with MMA because of a partial or complete inability of these individuals to convert methylmalonyl-CoA to succinyl-CoA in the tricarboxlic acid (TCA) cycle.

MMA is one of the **genetic disorders** that cause problems with mitochondrial metabolism. The mitochondria are the organelles inside cells that are responsible for energy production and respiration at the cellular level. One of the most important processes in the mitochondria is the TCA cycle (also known as the Krebs cycle). The TCA cycle produces the majority of the ATP (chemical energy) necessary for maintenance (homeostasis) of the cell. When blood sugar (glucose) is broken down in preparation to enter the TCA cycle, it is broken down into a chemical known as acetyl-CoA. It is this acetyl-CoA that is then further broken down in the TCA cycle to yield

KEY TERMS

Apoenzyme—An enzyme that cannot function without assistance from other chemicals called cofactors.

ATP—Adenosine triphosphate. The chemical used by the cells of the body for energy.

Cofactor—A substance that is required by an enzyme to perform its function.

Ketosis—An abnormal build-up of chemicals called ketones in the blood. This condition usually indicates a problem with blood sugar regulation.

Metabolic acidosis—High acidity (low pH) in the body due to abnormal metabolism, excessive acid intake, or retention in the kidneys.

Methylmalomic acid—An intermediate product formed when certain substances are broken down in order to create usable energy for the body.

Sudden infant death syndrome (SIDS)—The general term given to "crib deaths" of unknown causes.

TCA cycle—Formerly know as the Kreb's cycle, this is the process by which glucose and other chemicals are broken down into forms that are directly useable as energy in the cells.

carbon dioxide, water, and ATP. When some fatty acids and certain amino acids from proteins (specifically isoleucine, valine, threonine, methionine, thymine, and uracil) are broken down in preparation to enter the TCA cycle, they are broken down into propionyl-CoA, rather than acetyl-CoA. This propionyl-CoA is then converted into methylmalonyl-CoA, which is next converted to succinyl-CoA. It is succinyl-CoA that enters the TCA cycle to eventually yield carbon dioxide, water, and the ATP needed by the cells.

The conversion of methylmalonyl-CoA to succinyl-CoA involves the apoenzyme methylmalonyl-CoA mutase. An apoenzyme is an enzyme that cannot function without the aid of other chemicals (cofactors). One of the cofactors for this apoenzyme is cobalamin (vitamin B_{12}). Genetic MMA is a result of either a deficiency in the methylmalonyl-CoA mutase apoenzyme or a defect in the mechanism inside the cells that converts dietary vitamin B_{12} into its useable form for this chemical reaction.

An enzyme is a chemical that facilitates (catalyzes) the chemical reaction of another chemical or of other chemicals; it is neither a reactant nor a product in the chemical reaction that it facilitates. As a result, enzymes are not used up in chemical reactions; they are recycled. One molecule of an enzyme may be used to facilitate the same chemical reaction over and over again several hundreds of thousands of times. All the enzymes necessary for catalyzing the various reactions of human life are produced within the body by genes. In the case of the enzyme deficiency that causes MMA, the enzyme consists of a genetically produced apoenzyme and a cofactor (vitamin B_{12}) that comes from dietary sources.

Genetic profile

The **gene** responsible for MMA has been mapped to 6p21.2-p12. At least 30 mutations in this gene have been identified which lead to a broad spectrum of clinical symptoms and severities.

Demographics

The exact frequency of MMA is not known. It is believed to occur with a frequency of approximately one in every 48,000 live births in the United States. As in all recessive non-sex linked (autosomal) genetic disorders, both parents must carry the **gene mutation** in order for their child to have the disorder. Therefore, in cases where the parents are related by blood (consanguineous), the occurrence rate is higher than in the rest of the population. Parents with one child affected by MMA have a 25% likelihood that their next child will also be affected with MMA.

No increased likelihood for the disease on the basis of sex or ethnicity has been observed in cases of MMA.

Signs and symptoms

The abnormally high levels of acid in the blood of individuals affected with MMA can produce drowsiness, seizures, and in severe cases, coma and/or stroke. Prolonged acidemia can cause mental retardation. In the very rare instances of a complete apoenzyme absence, MMA is associated with sudden infant death syndrome (SIDS) and at least one known case of sudden child death at an age of 11 months.

Dehydration and failure to thrive are generally the first signs of MMA. These symptoms are generally accompanied by lethargy, lack of muscle tone (hypotonia), and "floppiness" in newborns.

Developmental delay is typically experienced in all individuals affected with MMA if treatment is not instigated early in life.

Some individuals affected with MMA have facial dysmorphisms. These include a broad nose, a high forehead, a skin fold of the upper eyelid (epicanthal folds), and a lack of the normal groove in the skin between the nose and the upper lip (the philtrum). In a few individuals affected with MMA, skin lesions resulting from yeast infections (candidosis) may be present, particularly in the mouth and facial area.

Occasionally, enlargement of the liver (hepatomegaly) is seen in MMA affected individuals.

Uncoordinated muscle movements (choreoathetosis), disordered muscle tone (**dystonia**), slurred speech (dysarthria), and difficulty swallowing (dysphagia), when observed in individuals affected with MMA may be signs of an acidemia-induced stroke.

Diagnosis

In newborns, a history of poor feeding, increasing lethargy, and vomiting are typical symptoms of MMA. In older infants, an episode of lethargy, often accompanied by seizures, is symptomatic. In children or adolescents, the symptoms may include muscle weakness, loss or diminishment of sensation in the legs, and/or blood clots.

Kidney (renal) disease may be observed in affected individuals with long untreated MMA.

A blood test to detect high levels of MMA is a decisive test for MMA. It may also be detected via a urine test for abnormally high levels of the chemical methylmalonate.

Prenatally, MMA may be diagnosed by measuring the activity of the apoenzyme methylmalonyl-CoA mutase in cultured cells grown from the cells obtained during an **amniocentesis**.

In one MMA-related case, a woman named Patricia Stallings was sentenced to life imprisonment for the presumed poisoning of her infant son with ethylene glycol, an ingredient in antifreeze. It was not until she gave birth in prison to a second son affected with MMA (and properly diagnosed) that forensic investigators discovered that the gas chromatography peak originally assigned to ethylene glycol (and used to convict Ms. Stallings) was, in fact, methylmalonic acid. All charges against Ms. Stallings were dropped and she was released from prison. This is an extreme case, but it certainly shows the importance of proper medical diagnosis of MMA.

Family history is often used to diagnose MMA when there are affected siblings or siblings that died shortly after birth for unclear reasons.

Treatment and management

Individuals affected with MMA are generally placed on low, or no, protein diets supplemented with carnitine and cobalamin (vitamin B_{12}) and alkalinizing agents (such as bicarbonate) to neutralize the excess acid caused by MMA. Intravenous administration of glucose may be necessary during acute attacks. In individuals who do not respond to carnitine and/or cobalamin, the anti-bacterial drug, metronidazole, may be prescribed. This drug kills some of the naturally occurring bacteria in the lower digestive tract and thereby reduces the production of propionate, a precursor chemical to methylmalonic acid.

In cases of severe MMA, kidney and/or liver transplants may be called for.

Prognosis

With appropriate care and diet, MMA is a controllable disease that offers no threat of death or permanent disability in patients beyond the first year of life. However, if unchecked, MMA can lead to permanent, irreversible disabilities or conditions, or even death. Some infants affected with extremely severe genetic mutations are stillborn or die prior to an appropriate diagnosis of MMA being made.

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Paul A. Johnson

Methylmalonicaciduria due to methylmalonic CoA mutase deficiency

Definition

Methylmalonicaciduria results from an autosomal recessive inherited genetic defect in methylmalonic CoA mutase (MCM), an enzyme required for the proper metabolism of some protein components, cholesterol, and fatty acids. As a result of a deficiency in MCM, methylmalonic acid accumulates in the bloodstream and urine, causing a severe metabolic disorder that may lead to death. Treatment consists chiefly of diet modification and the administration of several medications that may counteract this process.

Description

Proteins are important building blocks of the body, serving many different functions. They provide the structure of muscles, tissues, and organs, and regulate many functions of the human body. Proteins are made from amino acids obtained through the digestion of proteins (found in meats, dairy products, and other foods in the diet). Excess protein that is not required by the body can be broken down into its individual amino acid components. These amino acids can then be converted into glucose or directly enter metabolic pathways that supply the body with energy.

Each of the approximately 20 amino acids that are used to make human proteins are metabolized by specific biochemical reactions. Several of these amino acids (isoleucine, valine, threonine, methionine), as well as cholesterol and some fatty acids, share a common biochemical reaction in the pathway to conversion to usable energy. Each of these substances is converted to methylmalonic acid (also known as methylmalonic CoA), an intermediate product on the pathway leading to the production of usable energy.

In the next step of this biochemical pathway, methylmalonic acid is converted to succinic acid (also called succinyl CoA) by the enzyme, methylmalonic CoA mutase (MCM). In order for MCM to function properly, it also requires a vitamin B_{12}-derivative called adenosylcobalamin (when an enzyme requires another substance in order to perform its job, the helping substance is known as a coenzyme or cofactor).

When there is a defect or deficiency of MCM, methylmalonic acid cannot be converted into succinic acid and methylmalonic acid accumulates in high levels in the bloodstream (methylmalonicacidemia) and in the urine (methylmalonicaciduria). A deficiency in the cofactor, adenosylcobalamin, renders the MCM enzyme unable to perform its job, and will cause a similar effect. Abnormally high amounts of methylmalonic acid in the bloodstream causes a serious and dangerous metabolic condition that may lead to death.

The condition of methylmalonicacidemia was first described by V. G. Oberholzer in 1967 in infants critically sick with accumulations of methylmalonic acid in their blood and urine. An interesting historical note in respect to this disorder relates to the story of a woman named Patricia Stallings. In 1989, Ms. Stallings brought her son, Ryan, to the emergency room in St. Louis because he was very ill, and Ryan was noted to have high levels of acid in his bloodstream. Poisoning with ethylene glycol (antifreeze) also produces high levels of acid in the bloodstream. When Ryan later died, Ms. Stallings was sentenced to life in prison in January 1991, for the crime of murder by poisoning. However, while in prison the woman gave birth to a second son, who was diagnosed with the condition, methylmalonicacidemia. After discovering this diagnosis, scientists examined frozen samples of the first son's blood and determined that he, too, had methylmalonicacidemia which was responsible for his death. All charges against Ms. Stallings were dropped, and she was released from prison in September 1991. This is a dramatic illustration of the critical importance of proper diagnosis of complicated and rare **genetic disorders**.

Genetic profile

MCM deficiency is a genetic condition and can be inherited or passed on in a family. The genetic defect for the disorder is inherited as an autosomal recessive trait, meaning that two abnormal genes are needed to display the disease. A person who carries one abnormal **gene** does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to their children, who must inherit one disease gene from each parent to display the disease.

At least two forms of MCM deficiency have been identified. The disease genes are called, *mut0*, in which there is no detectable enzyme activity, and *mut-*, in which there is some, but greatly reduced, enzyme activity present. The gene for MCM is located on chromosome 6 (locus 6p21), and about 30 different mutations in the gene have been reported. Other mutations in pathways that produce the cofactor, adenosylcobalamin, exist and produce a condition similar to MCM deficiency.

Demographics

The incidence of all the conditions that cause methylmalonicacidemia was reported in a Massachusetts screening program at approximately one in 48,000 births. About half of the reported patients with methylmalonicacidemia have a deficiency of MCM *mut0* or *mut-*), as opposed to problems with the cofactor. Thus, incidence of specific MCM deficiency-related methylmalonicacidemia and aciduria in the general population may be estimated as one in 96,000. The geographical distribution of methylmalonicacidemia is not uniform and may be higher in certain ethnic groups. One report shows that the disorder is more common in the Middle East, probably occurring in one in 1,000 or 2,000 births. MCM deficiency is seen in equal amounts in males and females.

Signs and symptoms

The symptoms experienced by an infant with MCM deficiency vary with the type of mutation present. Infants born with the *mut0* type MCM deficiency will typically show more severe symptoms that manifest in the first 1-2 weeks of life, while infants with the *mut-* type MCM deficiency will have slightly milder symptoms that begin later in infancy.

Both sets of infants may show poor feeding, vomiting, lethargy, and low muscle tone, as well as a failure to grow at the normal rate. The disorder may first come to medical attention as it escalates into a full scale overwhelming attack, often triggered by intake of large amounts of dietary protein. If the condition has not yet been diagnosed, treatment is often poor, and patients may experience kidney damage, inflammation of the pancreas, or strokes that result in severe paralysis. More severe attacks can lead to seizures, coma, and eventually, death. As a result, newborns and infants with MCM deficiency may die early, even before a diagnosis can be reached.

If the infant survives the first attack, similar attacks may occur during an infection or following ingestion of a high-protein diet. Between episodes the patient may appear normal, but often, mild to moderate mental retardation will develop. Some infants with this disorder have characteristic facial features with a broad nose bridge, prominent lower eyelid folds, triangular mouth, and high forehead. Other symptoms of the disorder include frequent infections (especially yeast infections of the skin and mouth), enlarged liver, and low amounts of red blood cells. Often a family history is present for affected siblings or siblings that died very early in life for unclear reasons.

KEY TERMS

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are "essential amino acids" which the body cannot make and must therefore be obtained from food).

Antibiotics—A group of medications that kill or slow the growth of bacteria.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Cofactor—A substance that is required by an enzyme to perform its function.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Methylmalonic acid—An intermediate product formed when certain substances are broken down in order to create usable energy for the body.

Methylmalonic CoA mutase (MCM)—The enzyme responsible for converting methylmalonic acid to succinic acid, in the pathway to convert certain substances to usable energy.

Methylmalonicacidemia—The buildup of high levels of methylmalonic acid in the bloodstream due to an inborn defect in an enzyme.

Methylmalonicaciduria—The buildup of high levels of methylmalonic acid in the urine due to an inborn defect in an enzyme.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

A small percentage of people with the MCM deficiency apparently experience no symptoms or complications of the disease. For reasons not yet understood, these patients can tolerate a normal protein intake and accumulate high levels of methylmalonic acid in their body fluids without consequence.

Diagnosis

When symptoms such as those described above are encountered in a young infant or newborn, a diagnostic search for MCM deficiency should be considered. A routine blood test performed on almost all people who come to the hospital with severe illness will show high levels of acid in the bloodstream. Other clues to possible MCM deficiency include high levels of other substances in the bloodstream that appear with methylmalonicacidemia such as ketones and ammonia, or the presence of abnormally low amounts of glucose or red blood cells.

After high levels of acid in the bloodstream are noted, and if methylmalonicacidemia is suspected, samples of the urine and the blood will be taken and tested for the amount of methylmalonic acid. Abnormally high levels of methylmalonic acid suggest that MCM deficiency may be present. Genetic studies can then be performed to determine if any mutation in the MCM gene is present.

When the disease is diagnosed in a child, research laboratories can test unaffected siblings to determine if they are carriers of the mutant MCM gene. The same technology can be used to diagnose MCM deficiency before the birth of a child, by analyzing fluid or tissue from the sac surrounding the unborn fetus.

Treatment and management

Current research into a cure for MCM deficiency is focusing on the ability of liver transplantation or **gene therapy** to correct the abnormal MCM gene, however there is no cure for MCM deficiency at this time. The methods of treatment focus on three areas: diet/lifestyle modification, treatment with medications, and support during severe attacks of the disease.

Dietary changes include restriction of the amino acids that are converted to methylmalonic acid: methionine, threonine, valine, and isoleucine. As a result, people with MCM deficiency are limited to a low protein diet that provides the minimum natural protein needed for growth. Calcium and multivitamin supplements should also be taken to correct any nutritional deficiencies that result from avoiding high-protein foods. Activity in children with MCM deficiency need not be restricted.

People with MCM deficiency may benefit from several medications when taken daily. The antibiotic, metronidazole, kills bacteria that live in the intestine and produce substances that are converted to methylmalonic acid. The supplement, L-carnitine, is often used to reduce some of the toxic effects of high levels of methylmalonic acid. Although most reports state that there is no benefit from vitamin B_{12} supplementation, a few reports suggest that a trial of vitamin B_{12} may be reasonable to determine if it will result in improved MCM function. Finally, bicarbonate can be used to counteract low levels of acid that persist in the bloodstream.

All of the above medications can be used to aid in treatment of a severe attack of methylmalonicacidemia. In addition, a patient in crisis should be given excessive amounts of intravenous fluids, to help clear methylmalonic acid from the circulation. Special blood filtering machines can be used when levels of methylmalonic acid or ammonia become dangerously high. Stressful situations that may trigger attacks (such as infection) should be treated promptly.

Patients with MCM deficiency should be seen regularly by a team of health care specialists including a primary care provider, a dietician, and a biochemical geneticist who is familiar with the management of the disease. Parents should be educated in the signs and symptoms of impending attacks and how to respond appropriately. Close monitoring of amino acid levels, urinary content of methylmalonic acid, and growth progress is necessary to ensure proper balance in the diet and the success of therapy.

Prognosis

Prognosis depends on early and accurate diagnosis of the disease and the prompt initiation of diet modification and medications. In those infants who escape early diagnosis, the prognosis is poor as severe attacks will lead to complications as extreme as sudden death. In those infants that do survive initial attacks, damage to the developing brain and kidneys may result that leave the child severely incapacitated.

The addition of the medications, L-carnitine and metronidazole, to the management of this disorder has changed the prognosis. Scientists point out that although most patients before 1985 died, those after 1985, when these drugs were introduced, survived with improved general health. Thus, if detected early and treated appropriately, the lifestyle of a well-managed patient with MCM deficiency can be relatively normal, without mental retardation or growth delay.

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Oren Traub, MD, PhD

Microcephaly with spastic diplegia selmanona syndrome I *see* **Paine syndrome**

Microcephaly-mental retardation-tracheoesophageal fistual syndrome *see* **Oculo-digito-esophago-duodenal syndrome**

Microcephaly-mesobrachyphalangy-tracheo-esophagael fistula syndrome (MMT) *see* **Oculo-digito-esophago-duodenal syndrome**

Microphthalmia with linear skin defects (MLS)

Definition

Microphthalmia with linear skin defects (MLS) is a rare genetic disorder that causes abnormalities of the eyes and skin. This disorder was first recognized as a distinct genetic condition in 1990.

Description

MLS is a rare disorder that is observed only in females because males with the disease do not survive to birth. This disorder is also called MIDAS (Microphthalmia, dermal aplasia, and sclerocornea) syndrome. People affected by MLS have:

- small sunken eyes (microphthalmia),
- irregular red streaks of skin on the head and neck (skin erythema),
- and abnormal development of the sclera and cornea of the eye.

The eye is composed of three layers: the sclera, the choroid, and the retina. The sclera is the tough white outer coat of the eyeball. As this coat passes over the lens, it normally becomes clear. This clear portion of the sclera is the cornea. Both the sclera and the cornea are affected by MLS.

The choroid is the middle layer of the eye. It serves to nourish the retina and absorb scattered light. The retina is the inner, light-sensitive, layer of the eye. The retina receives the image transmitted by the lens and it contains the rods and cones that are responsible for color vision and vision in dim light. Both the choroid and the retina are unaffected by MLS.

Genetic profile

The **gene** responsible for MLS has been localized to a portion of the short arm (p) of the X chromosome (Xp22.3). The specific symptoms of MLS are believed to result from the premature cutoff (terminal deletion) of the X chromosome at this point. People with MLS do not have the portion of the short arm of the X chromosome beyond the Xp22.2 location.

KEY TERMS

Cornea—The transparent structure of the eye over the lens that is continous with the sclera in forming the outermost, protective, layer of the eye.

***de novo* mutation**—Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

Microphthalmia—Small or underdeveloped eyes.

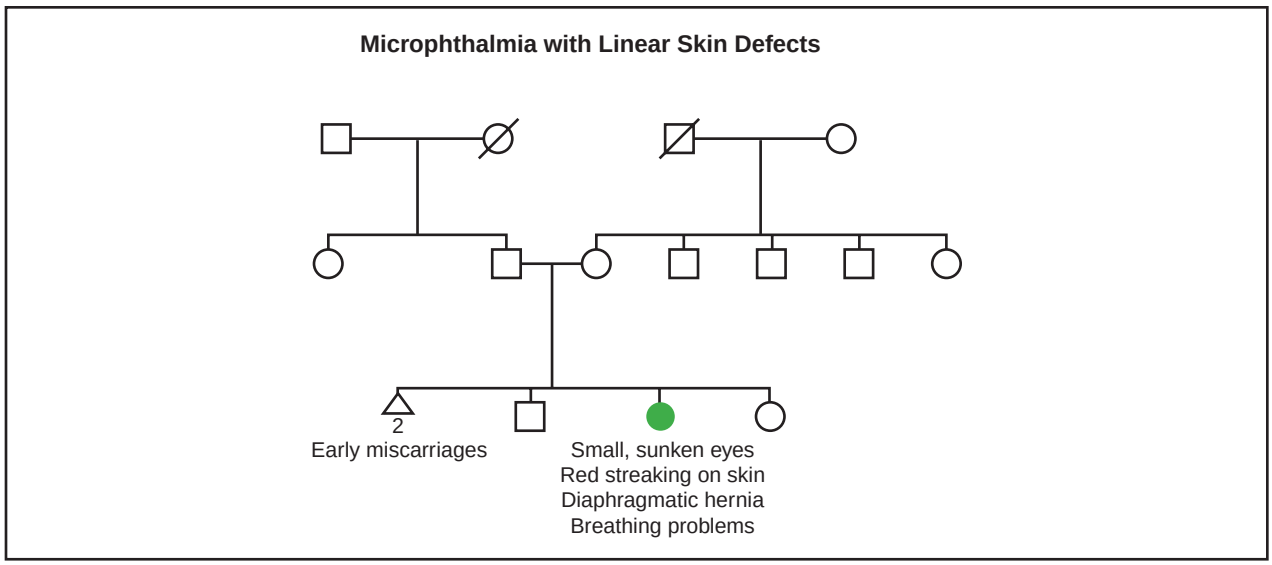
Orbital cysts—Small fluid-filled sacs that abnormally develop inside the bony cavity of the skull that holds the eyeball.

Sclera—The tough white membrane that forms the outer layer of the eyeball.

Septum pellucidum—A membrane between two of the normal cavities of the brain that prevents electrical signals from passing between different portions of the brain.

Skin erythema—Irregular red streaks of skin.

Terminal deletion—The abnormal early termination of a chromosome caused by the deletion of one of its ends.



(Gale Group)

Nearly all of the cases of MLS are believed to result from *de novo* mutations since parents of affected individuals do not carry the MLS mutation in their **chromosomes**. A *de novo* mutation is caused by a problem with the chromosomes of the parental egg or sperm cells. The remainder of the chromosomes in the parents are not affected. As the sex cells of one of the parents reproduce, an error occurs. This leads to the transmission of a new mutation from that parent to his or her child. This mutation is expressed for the first time in the child of that parent.

A typical female has two X chromosomes. A typical male has one X chromosome and one Y chromosome. Because no XY male has ever been diagnosed with MLS, it is assumed that MLS is dominant and X-linked with 100% fetal mortality in males. This type of genetic disorder is also called an X-linked male-lethal trait.

There have been a few reported cases of males affected with MLS. These individuals presumably survived because they were XXY males (genetically female with ambiguous or male sex organs), rather than the typical male with XY chromosomes. This condition (XXY) is called **Klinefelter syndrome**.

Demographics

Approximately 300 individuals, all without a Y chromosome, have been diagnosed with MLS worldwide. MLS is not associated with any particular sub-populations. It appears with equal frequency in all races and across all geographies. Because it is an X-linked male-lethal trait, it is observed exclusively in females or, in a few cases, in XXY males.

Signs and symptoms

MLS is characterized by:

- small, sunken, eyes (microphthalmia);
- defects of the sclera and cornea portions of the eye
- linear red streaking of the skin on the upper body, primarily the head and neck;
- abnormal protrusion of the abdominal contents upward through an opening in the diaphragm (diaphragmatic hernia), which causes difficulty with breathing (respiratory distress);
- a lack of the transparent membrane (septum pellucidum) in the brain that forms a wall between two of the normal cavities (the lateral ventricles) of the brain;
- and, a condition in which the heart is located on the right side, rather than the left side, of the chest (dextrocardia).

In individuals affected with MLS, the bony cavity that contains the eyeball (orbit) often contains small fluid-filled sacs (orbital cysts). The sclera is often not fully or properly formed, and the cornea generally has areas that are opaque rather than transparent. This corneal opacity causes blurring of vision and may result in blindness. Corneal opacities should not be confused with cataracts, which are opacities of the lens of the eye, not of the cornea.

Difficulty in breathing (respiratory distress) is seen at birth in some patients with MLS. This is caused by a hole in the muscle beneath the lungs (diaphragm) that is responsible for the flow of air into and out of the lungs. This condition will rapidly lead to death if it is not surgically repaired.

Seizures and mental retardation have been observed in some MLS patients. It is believed that these individuals do not have a septum pellucidum. The absence of this membrane may allow electrical transmissions between parts of the brain that are usually isolated from each other. These inadvertent electrical signals may cause the seizures and the mental retardation that is sometimes seen in MLS patients.

Diagnosis

MLS is generally diagnosed by the presence of the characteristic red striping of the skin on the head and neck accompanied by small eyes (microphthalmia) and opaque patches on the corneas.

MLS is differentiated from **Goltz syndrome**, which has a similar gene locus, in that the patient with MLS has skin irregularities only on the upper half of the body, most typically only on the head and neck. Goltz syndrome tends to result in skin irregularities across their entire bodies. Also, patients with MLS do not have the abnormal fatty tissue deposits seen under the skin of Goltz syndrome patients. Finally, MLS does not have the clefting of the hands or feet (syndactyly) or incomplete formation of certain structures of the eyes (**coloboma**) seen in Goltz syndrome.

In early 2001, prenatal diagnosis for MLS syndrome was not yet available, but identification of the gene responsible for MLS makes **genetic testing** for this dominant trait potentially possible.

Treatment and management

The treatment and management of MLS is directed toward the symptoms seen in each patient. All those affected with MLS will need eye care including surgeries to potentially repair damaged areas of the cornea and sclera. Some individuals may require skin care treatments depending on the severity of the skin abnormalities.

In cases of patients with a diaphragmatic hernia, emergency surgery shortly after birth may be necessary to attempt to repair the damaged area. Unfortunately, most cases of this type of hernia cannot be surgically corrected and the patient will die.

In cases of patients with a lack of the septum pellucidum in the brain, anti-seizure medication may be necessary to control the seizures.

Prognosis

MLS is lethal in males prior to birth. In females, a full life expectancy is possible if the complications are not severe and if medical treatment is followed.

Most problems of the cornea and sclera of the eye associated with MLS can be treated with corrective lenses or potentially surgically repaired with corneal implants or laser surgery.

Seizures, if present, can generally be controlled by anti-seizure medications.

Developmental delays in growth, motor ability, speech, and intellect occur in some, but not all, cases of MLS. The amount of delay that is observed is directly related to the severity of seizure activity in the brain caused by the malformation, or lack, of the septum pellucidum.

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Paul A. Johnson

MIDAS syndrome *see* **Microphthalmia with linear skin defects**

Mild hypophosphatasin *see* **Hypophosphatasia**

Miller-Dieker syndrome

Definition

Miller-Dieker syndrome (MDS) is a rare genetic disorder. Its signs and symptoms include severe abnormalities in brain development as well as characteristic facial features. Additional birth defects may also be present.

Description

MDS was named for the two physicians, J. Miller and H. Dieker who independently described the condition in the 1960s. The hallmark of MDS is lissencephaly (smooth brain), a condition in which the outer layer of the brain, the cerebral cortex, is abnormally thick and lacks the normal convolutions (gyri). In some areas of the brain, gyri are fewer in number but wider than normal (pachygyri). Other areas lack gyri entirely (agyri). Normally, during the third and fourth months of pregnancy, the brain cells in the baby multiply and move to the surface of the brain to form the cortex. Lissencephaly is caused by a failure of this nerve cell migration. MDS is often called Miller-Dieker lissencephaly syndrome.

Genetic profile

When MDS was first described, geneticists thought it followed an autosomal recessive pattern of **inheritance**. However, in the early 1990s, several patients with MDS were found to be missing a small portion of the short arm of chromosome 17 (17p13.3). This is called a partial deletion of chromosome 17. MDS is now classified as a "micro-deletion syndrome" because it is the result of the absence of genes that are normally located in this region of chromosome 17. In 1993, research scientists identified one of the genes in this region. They named it LIS1 for "first lissencephaly gene" because it appeared to be important in normal brain formation. The main evidence for this was that the LIS1 **gene** was missing in a number of individuals with isolated lissencephaly; that is, lissencephaly without the additional characteristics found in MDS. Researchers then studied a number of patients with MDS and found over 90% of them were missing the LIS1 gene as well as other, as yet unidentified genes, on the short arm of chromosome 17. Geneticists now think that the characteristic facial appearance and other abnormalities seen in MDS are due to the deletion of these other genes. For this reason, MDS has also been described as a "contiguous gene syndrome".

Most genes, including all genes on the autosomes (non-sex **chromosomes**), are normally present in pairs. Individuals with MDS who have a micro-deletion of a small region of the short arm of one copy of their chromosome 17 still have one normal copy of this chromosome region on their other chromosome 17. For this reason, MDS is said to be due to "haploinsufficiency," the term for a genetic condition caused by the lack of function of only one of the two copies of a gene. As with other haploinsufficiency syndromes, MDS has also been described as having an autosomal dominant pattern of inheritance.

Individuals with MDS usually die in infancy. Because they do not live to the age where they can reproduce, they cannot transmit MDS to their offspring. Eighty percent of individuals with MDS have it as the result of a new (*de novo*) deletion of a small part of the short arm of one chromosome 17 in just the one egg or sperm that formed that individual. The parents of these affected individuals have normal chromosomes without deletions. This means that their risk of having another child with MDS is very low (probably less than 1%). However, the other 20% of those with MDS have the syndrome because one of their parents carries a rearrangement of one copy of their own chromosome 17. The rearrangement can be an inversion or a balanced translocation between chromosome 17 and one of the other chromosomes. Since the rearrangement is balanced; that is, all the chromosome material is present but in a rearranged form, the parent is normal. However, when that parent produces an egg or a sperm, the balanced chromosome rearrangement can go through a further rearrangement. This results in a portion of the short arm of chromosome 17 being deleted. The individual who develops from that egg or sperm will have MDS.

Demographics

MDS is present in fewer than one in 100,000 births. There is no information to suggest that the syndrome is more common in any particular ethnic or racial group.

Signs and symptoms

Infants with MDS are usually small at birth. Characteristic facial features may include a high forehead with furrows and vertical ridges, indentation of the temples, a small, upturned nose, up-slanting eyes, a small mouth, a thick, broad upper lip with a thin border, low-set ears, and occasionally, a cleft palate. Some infants with MDS also have birth defects involving the heart and kidneys. Signs and symptoms can vary among MDS patients. This may relate to the actual size or exact location of the chromosome 17 deletion in that individual.

MDS infants have a very limited capacity for development due to the lissencephaly and associated brain abnormalities. Mental retardation is severe to profound.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

CAT (CT) scan—Computerized (axial) tomography. A special x ray technique used to examine various tissues, particularly the brain, in great detail.

Cerebral cortex—The outer surface of the cerebrum made up of gray matter and involved in higher thought processes.

Chorionic villus biopsy—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Contiguous gene syndrome—A genetic syndrome caused by the deletion of two or more genes located next to eachother.

FISH (fluorescence *in situ* hybridization)—Technique used to detect small deletions or rearrangements in chromosomes by attempting to attach a fluorescent (glowing) piece of a chromosome to a sample of cells obtained from a patient.

Gastrostomy—The construction of an artificial opening from the stomach through the abdominal wall to permit the intake of food.

Haploinsufficiency—The lack of one of the two normal copies of a gene. Haploinsufficiency can result in a genetic disorder if normal function requires both copies of the gene. Haploinsufficiency is one explanation for a dominant pattern of inheritance.

Hypotonia—Reduced or diminished muscle tone.

Inversion—A type of chromosomal defect in which a broken segment of a chromosome attaches to the same chromosome, but in reverse position.

Lissencephaly—A condition in which the brain has a smooth appearance because the normal convolutions (gyri) failed to develop.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Micro-deletion syndrome—A collection of signs and symptoms caused by a deletion of a gene or genes that is too small to be seen through the microscope.

Microcephaly—An abnormally small head.

Opisthotonos—An arched position of the body in which only the head and feet touch the floor or bed when the patient is lying on their back.

Prenatal diagnosis—The determination of whether a fetus possesses a disease or disorder while it is still in the womb.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

X-linked—Located on the X chromosome, one of the sex chromosomes. X-linked genes follow a characteristic pattern of inheritance from one generation to the next.

Infants with MDS may be able to do little more than roll over. Convulsions (seizures) develop within a few weeks of birth and can be severe. Most newborns with MDS have low muscle tone (hypotonia), but later develop stiffness (spasticity) and an arching of the body (opisthotonos). Poor feeding leads to a failure to thrive and increases the risk of pneumonia because the infants can accidentally inhale baby formula into their lungs. Head size is usually in the normal range at birth, but poor brain growth means that, by the age of one year, the children have a smaller-than-normal head size (microcephaly).

Diagnosis

MDS is not the only disorder associated with lissencephaly. Autosomal dominant, autosomal recessive, and X-linked patterns of inheritance have been described among the more than two dozen genetic syndromes featuring this brain abnormality. Less commonly, lissencephaly can also be the result of fetal infections such as prenatal cytolomegalovirus (CMV). An accurate diagnosis of MDS is important not only because it can provide a prognosis for the affected child, but because it can give parents an estimate of their risk for having another child with MDS.

MDS may be suspected in the newborn period if an infant has the characteristic facial features along with low muscle tone. Studies of the infant's brain by CAT scan or MRI will show the smooth brain surface. After the diagnosis of MDS is made on the basis of these signs and symptoms, it is very important to study the infant's chromosomes to check for the characteristic chromosome 17 deletion. This is done by sending a small sample of the infant's blood to a cytogenetics laboratory. Trained laboratory personnel (cytogeneticists) first examine the infant's chromosomes through the microscope using traditional techniques. If no deletion or other chromosome rearrangement is detected in this step, newer methods can be used to search for deletions that are too small to see by ordinary means (micro-deletions). A special technique called FISH (fluorescent in situ hybridization) can detect chromosome regions where very small pieces of **DNA** are missing. This test is usually done on the same blood sample.

Carrier detection

When a chromosome deletion is found in an infant, both parents' chromosomes should also be studied to determine if one of them carries a chromosome rearrangement such as a balanced translocation. Although most parents of infants with MDS have normal chromosomes, in approximately 20% of children, one parent will have a chromosome rearrangement, which can increase the risk for having another child with MDS. Other family members should also be offered chromosome studies because these balanced chromosome rearrangements can be passed down through a family undetected, and, thus, other family members may be carriers. The first step in studying other family members is for a geneticist or genetic counselor to obtain a detailed family history and construct a pedigree (family tree) to determine which family members should be offered testing.

Prenatal diagnosis

If a couple has had one child with MDS, they can be offered prenatal diagnosis in future pregnancies. This option is particularly important for the 20% of MDS families where one parent carries a balanced chromosome rearrangement. The risk for these couples to have another affected child depends on the exact type of chromosome rearrangement present and may be as high as 25-33%. For families in which both parents' chromosomes are normal, the risk of having another child with MDS is low (1% or less). Either chorionic villus sampling (CVS) or **amniocentesis** can be used early in a pregnancy to obtain a small sample of cells from the developing embryo for chromosome studies. Early prenatal diagnosis by ultrasound is not reliable because the brain is normally smooth until later in pregnancy. Couples who are considering prenatal diagnosis should discuss the risks and benefits of this type of testing with a geneticist or genetic counselor.

Treatment and management

There is no cure for MDS and treatment is usually directed toward comfort measures. Because of the feeding problems and risk of pneumonia, surgeons often place a tube between the stomach and the outside of the abdomen (gastrostomy tube). Feedings can be made through the tube. Seizures are often difficult to control even with medication.

Prognosis

Death often occurs in the first three months of life and most infants with MDS die by two years of age, although there have been reports of individuals living for several years.

Resources

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ORGANIZATIONS

Lissencephaly Network, Inc. 716 Autumn Ridge Lane, Fort Wayne, IN 46804-6402. (219) 432-4310. Fax: (219) 432-4310. lissennet@lissencephaly.org. <http://www.lissencephaly.org>.

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<http://www.kumc.edu/gec/support/lissence.html>.

Sallie Boineau Freeman, PhD

Mirhosseini-Holmes-Walton syndrome *see* **Cohen syndrome**

MODY—Maturity-onset diabetes of the young *see* **Diabetes mellitus**

KEY TERMS

Balanced chromosome translocation—A rearrangement of the chromosomes in which two chromosomes have broken and exchanged pieces without the loss of genetic material.

Cranial nerves—The twelve nerves that originate in the brain, and control functions such as hearing, vision and facial expression.

Möebius syndrome

Definition

Möebius syndrome is a condition in which the facial nerve is underdeveloped, causing paralysis or weakness of the muscles of the face. Other nerves to the facial structures may also be underdeveloped.

Description

Möebius syndrome has been called "life without a smile" because the paralysis of the facial muscles, the most constant feature, leads to the physical inability to form a smile even when happy feelings are experienced. The facial nerve is one of a group of 12 nerves known as the cranial nerves because they originate in the brain. The facial nerve is also known as the seventh cranial nerve. The sixth cranial nerve, also called the abducens, controls blinking and back-and-forth eye movement and is the second most commonly affected cranial nerve in Möebius syndrome. Additional cranial nerves affected in some patients control other eye movements and other functions such as hearing, balance, speech, and feeding.

Individuals with Möebius syndrome may also have abnormalities of their limbs, chest muscles, and tongue. The chance of mental retardation appears to be increased in people with Möebius syndrome, but most people with the disorder have normal intelligence.

Genetic profile

Most cases of Möebius syndrome are isolated and do not appear to be genetic, but occurrence in multiple individuals within some families indicates that there are multiple genetic forms. One study in 1991 suggested that forms of Möebius syndrome which included abnormalities of the limbs and skeleton were less likely than other types to be genetic. During pregnancy, certain exposures, such as to the drug misoprostol, appear to increase the risk of Möebius syndrome.

Chromosomes 13, 3, and 10 appear to contain genes causing forms of Möebius syndrome, now named, respectively, types 1, 2, and 3. The presence of a **gene** on chromosome 13 was first suggested based on a family in which several members had facial weakness and finger abnormalities along with a chromosome rearrangement called a balanced translocation involving chromosomes 1 and 13. In a balanced translocation, two chromosomes have broken and exchanged pieces. Balanced translocations are usually not associated with physical abnormalities unless (1) material has been lost or gained during the breaks, or (2) a gene is disrupted by one of the breaks. When a child with Möebius syndrome in an unrelated family was found to have a deletion (missing piece) of chromosome 13 in the same area as the break in the first family, this suggested that there might be a gene causing Möebius syndrome on chromosome 13 rather than on 1.

The genes on chromosomes 3 and 10 were localized using a technique called linkage mapping, which involves using molecular genetics and statistical methods to look throughout all of the chromosomes in families with several affected members for areas associated with the disease. As of 2001, the actual genes on chromosomes 3, 10, and 13 have not been identified. These three forms of the disease are inherited in an autosomal dominant manner, which means that only one altered copy of the gene is required to have the disease, and people with the disease have a 50% chance of having an affected child with each pregnancy. However, in the chromosome 3 and 10 families, some individuals who appear to carry a gene do not show signs of Möebius syndrome, suggesting that factors other than genetics, such as uterine environment, are involved even in these highly familial cases.

One family was reported in which two brothers and their male cousin who were the sons of sisters all had Möebius syndrome along with other physical abnormalities and mental retardation. Boys only have one X chromosome and can inherit an X-linked disease from their unaffected mothers, who have two X chromosomes. The

pattern of affected children in this family is therefore typical of X-linked **inheritance**, so it is suggested that there may be a gene involved in Möebius syndrome on the X chromosome as well. If this is the case, the son of a woman with an altered Möebius gene on one X-chromosome would have a 50% chance of inheriting the gene and having the condition. A man with this type of Möebius syndrome would be unlikely to have affected children since his daughters would likely have one normal X chromosome from their mother and his sons would not receive his X chromosome but his Y chromosome. In another family, a brother and sister with unaffected parents had Möebius syndrome, suggesting autosomal recessive inheritance, in which two altered copies of a gene are required to have the disorder. In an autosomal recessive disorder, a couple in which each parents carry one altered copy of the disease gene have a 25% chance of having a child with the condition with each pregnancy.

Demographics

Möebius syndrome is extremely rare and does not seem to affect any particular ethnic group more than others. The families in which genes on chromosomes 3 and 10 were mapped were Dutch.

Signs and symptoms

The first sign of Möebius syndrome in newborns is an inability to suck, sometimes accompanied by excessive drooling and crossed eyes. Also seen at birth in some patients are abnormalities of the limbs, tongue, and jaw. Children also often have low muscle tone, particularly in the upper body. The lack of facial expression and inability to smile become apparent as children get older.

When cranial nerve palsy is associated with limb reduction abnormalities and the absence of the pectoralis muscles, the condition is known as Poland-Möebius or Möebius-Poland syndrome. Common limb abnormalities are missing or webbed fingers and **clubfoot**.

The prevalence of mental retardation in Möebius syndrome is uncertain. It has been estimated in the past to be between 10% and 50%, but these numbers are thought to be overestimates resulting from the lack of facial expression and drooling seen in people with Möebius syndrome. In one study of familial cases of Möebius syndrome, 3% were reported to be mentally retarded.

Diagnosis

Diagnosis of Möebius syndrome is made on the basis of clinical symptoms, especially the lack of facial expression. Since exact genes involved in Möebius syndrome have not yet been identified as of 2001, molecular **genetic testing** is not available at this time.

Treatment and management

The ability to smile has been restored in some cases of Möebius syndrome by surgery which transfers nerve and muscle from the thigh to the face. Other surgeries can be used to treat eye, limb, and jaw problems. In children with feeding problems, special bottles or feeding tubes are used. Physical and speech therapy are used when necessary to improve control over coordination, speech, and eating.

Prognosis

Möebius syndrome does not appear to affect life span, and individuals who are treated for their symptoms can lead normal lives.

Resources

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Toni I. Pollin, MS, CGC

Mohr syndrome *see* **Oral-facial-digital syndrome (OFD)**

Morquio syndrome (MPS IV) *see* **Mucopolysaccharidosis (MPS)**

Moyamoya

Definition

Moyamoya is a progressive syndrome characterized by narrowing of the blood vessels in the brain. Moyamoya is the Japanese term for ‘cloud of smoke drifting in the air.’

Description

The term moyamoya is used to describe how the arteries in the brain look in this syndrome, which was

first described in the 1950s. There is no clear cause for this disease. It can be caused genetically, but can also occur as a result of having other diseases. Moyamoya is seen in patients with a variety of diseases, including: **neurofibromatosis**, trisomy 21 (**Down syndrome**), sickle cell disease, chronic meningitis, and as a side effect of irradiation.

Moyamoya is a disease of the blood vessels in the brain. The carotid arteries are two of the large arteries that allow blood to flow into the brain. The external carotid artery allows blood to reach areas within the neck, while the internal carotid artery travels to the brain and branches off into smaller vessels to reach all areas of the brain. In patients with moyamoya, there is a symmetric thinning of the width of the internal carotid arteries. The brain responds to this thinning by making the smaller blood vessels bigger, trying to get blood to the areas of the brain that are not getting enough. When dye is injected into the arteries of the brain (a cerebral angiogram), a characteristic pattern is seen. On the angiogram, this looks like a cloud of smoke.

KEY TERMS

Angiography—Injecting dye into blood vessels so they can be be seen on a radiograph or picture.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Stroke—A sudden neurological condition related to a block of blood flow in part of the brain, which can lead to a variety of problems, including paralysis, difficulty speaking, difficulty understanding others, or problems with balance.

Genetic profile

The primary form of moyamoya is seen most often in Japan. Studies have found the familial form to account for 7–10% of the cases. A recent study focused on 16 families in order to find the genetic marker for the disease. The **gene** locus was found to be present on the short arm of chromosome 3, specifically 3p26–p24.2. Other studies have found possible involvement of genes on **chromosomes** 6 and 17 as well.

Demographics

Although the disease seems to occur most often in Japanese people, patients have been found throughout the world. It is thought that one in a million people are affected each year. The age of onset of the disease has two peaks, the first being in children under 10 years old, and the second in adults in their 20s–40s. Fifty percent of moyamoya cases are found in patients younger than ten years of age. Females seem to have moyamoya more often than males. The female-to-male ratio is 3:2.

Signs and symptoms

The first signs and symptoms of moyamoya tend to be different in children and adults. Children most often present with a sudden seizure or a stroke. Strokes can cause weakness on one side of the body. These are often brought on with exercise or fast breathing. Less severe strokes, called transient ischemic attacks (TIAs), can occur very often. During these TIAs, the weakness in the body is temporary and will not last more than a few hours. But, over a period of years, strokes and TIAs will leave patients with permanent weakness on both sides of the body, seizure disorders, and mental retardation. While children will present with seizures or strokes, adults tend to present with intracerebral hemorrhage (bleeding within the brain). Depending on where the bleeding or strokes occur, there can be a variety of chronic symptoms including: speech disturbance, visual disturbance, headaches, difficulties with sensation and involuntary movements (moving parts of the body when you do not intend to).

Diagnosis

Cerebral angiography is the main method of diagnosis. Today, this is the best way to see the arteries in the brain and to assess their level of occlusion (blockage). Other methods of imaging have been used in an attempt to diagnose moyamoya. High resolution imaging such as computed tomography scans (CT scans) do not show findings specific to this syndrome. However, areas of old strokes or bleeding can be seen. Magnetic resonance imaging (MRI) is also very sensitive at looking for old areas of stroke but cannot show which blood vessels may be blocked as compared with angiography. These non-invasive imaging techniques may however, provide clues for the diagnosis. The doctor would then recommend angiography to confirm the diagnosis.

Treatment and management

There is no one best treatment for moyamoya. Medical therapy consists of drugs that prevent blood

clot formation such as aspirin. Drugs that help dilate the narrowed blood vessels, such as calcium channel blockers, are also used. Calcium channel blockers that have been successful include nicardipine and verapamil. These calcium channel blockers may also help with the headaches that some patients may get during the course of their illness.

Many different surgical approaches have been used to help improve blood flow in these patients. It is not known what the long term outcome of these procedures are. As of 2001, the most popular operations are: encephaloduroanteriosynangiosis (EDAS), encephalomyosynangiosis (EMS), and superficial temporal artery-middle cerebral artery (STA-MCA) anastamosis.

In EDAS, an artery that sits under the scalp called the superficial temporal artery, is separated from the skin. A small opening in the skull is then made. The artery from the scalp is then sewn into the surface of the brain. The piece of skull that was removed is then put back in place to protect the new connection. This procedure has also been termed pial syngiosis.

In the EMS procedure, a muscle overlying the temple region of the forehead, called the temporalis muscle, is detached. Once again, an opening in the skull is made and the muscle is placed on the surface of the brain.

In the STA-MCA operation, the scalp artery is directly connected to an artery in the brain. All of the these surgical procedures attempt to provide blood to areas of the brain that are not getting enough. Although symptoms may be improved soon after surgery, it usually takes months for the new blood vessels to form.

Prognosis

It is unclear what the long-term risk for complications is in people with moyamoya disease. A study published in 2000 looked at 334 patients with moyamoya disease diagnosed between 1976 and 1994. Approximately 60% of the adults who had moyamoya had a cerebral hemorrhage at some point. Approximately 60% of the children who had moyamoya had a stroke or TIA at some point. Cerebral hemorrhage was found to be the most important factor that predicted a poor outcome. The overall effect of medical and surgical treatment on long term outcomes is not well known at this time.

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David E. Greenberg, MD

Mucolipidosis

Definition

Mucolipidosis (ML) is a group of rare, inherited disorders that are characterized by the accumulation of complex fats, called mucolipids, in the cells of the body. The symptoms range from skeletal abnormalities and vision problems to physical and mental retardation.

Description

Types of mucolipidosis

There are three major types of mucolipidosis. Mucolipidosis II (ML II, ML2) or ML disorder type II, is known as I-cell disease (ICD). Sometimes it is called Leroy disease, after Jules Leroy who described the disorder in 1969. ML II also is known as N-acetylglu-

cosamine-1-phosphotransferase (GNPTA) deficiency. GNPTA is the enzyme that is defective in ML II.

Mucolipidosis III (ML III, ML3), or ML disorder III, is a milder form of ML II. In ML III, the enzyme GNPTA has reduced activity; whereas it has no activity in ML II. ML III was first described in 1966. It is often called pseudo-Hurler polydystrophy because its symptoms resemble a mild form of the mucopolysaccharide disorder known as **Hurler syndrome**. It is a polydystrophy because several systems of the body are affected.

In the past, ML II and ML III were classified as mucopolysaccharidoses (MPS II and MPS III, respectively). MPS is a condition in which complex sugars called mucopolysaccharides accumulate in the cells of the body. Although this may occur in ML, excess amounts of mucopolysaccharides are not excreted in the urine, as they are in MPS.

Mucolipidosis IV (ML IV, ML4) was first described in 1974. It also is called ML disorder IV, Berman syndrome, or sialolipidosis.

Neuraminidase deficiency originally was classified as mucolipidosis I (ML I). However, neuraminidase deficiency does not involve the accumulation of mucolipids.

Lipids

Lipids are large, complex biomolecules that are very important components of cell membranes. They also are used to store energy and are present in mucus secretions.

Lipids are continually broken down and replaced. This breakdown of lipids occurs in a membrane-bound compartment or organelle within cells, called the lysosome. The lysosome contains many enzymes that break down the lipids. These enzymes are produced outside of the lysosome and have to be transported into the organelle. The enzyme GNPTA attaches a signal to these enzymes that directs them to the lysosome.

Lysosomal storage diseases

MLs are classified as lysosomal storage diseases because the lysosomes accumulate lipids that cannot be broken down. Eventually, the lysosomes become so filled with lipids that the cells form structures called inclusion bodies to contain the lipids. Inclusion bodies give the cells a characteristic appearance. The name "I-cell disease" refers to these inclusion bodies.

Individuals with ML II or ML III have little or no GNPTA enzyme activity. Thus, the lysosomal enzymes cannot reach the lysosome to help break down lipids. ML II and ML III are caused by mutations, or changes, in one of the genes that encodes a part of GNPTA. A disorder called mucolipidosis III, variant form, or complementation group C, is caused by a mutation in a **gene** that encodes a different part of GNPTA. However, the symptoms of this form of ML III are very similar to those of the more common type of ML III.

ML IV is caused by a mutation in the gene encoding a protein called mucolipin-1. In ML IV, membrane lipids and mucopolysaccharides accumulate in the lysosomes

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Epicanthal fold—Fold of skin extending from the eyelid over the inner corner of the eye.

Hydrolase—Enzyme that uses water to break down substances.

Inclusion body—Abnormal storage compartment inside a cell.

Lipid—Large, complex biomolecule, such as a fatty acid, that will not dissolve in water. A major constituent of membranes.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mucolipid—Lipid that accumulate in cells in mucolipidosis disorders.

Mucolipin-1—Protein in the cell membrane, probably a calcium ion channel, involved in recycling membrane lipids and is deficient in mucolipidosis IV.

Mucopolysaccharide—A complex molecule made of smaller sugar molecules strung together to form a chain. Found in mucous secretions and intercellular spaces.

N-acetylglucosamine-1-phosphotransferase (GNPTA)—Enzyme that attaches a signal to other enzymes and directs those enzymes to the lysosome; deficient in mucolipidoses II and III.

of cells throughout the body. Apparently, in the absence of mucolipin-1, these substances are transported to the lysosome rather than recycled to the cell membrane.

Genetic profile

All of the MLs are inherited as autosomal recessive traits. They are autosomal because the genes that are responsible for these disorders are located on autosomal **chromosomes**, rather than on the X or Y sex chromosomes. The traits are recessive because they are only expressed in individuals who have inherited two copies of the gene that causes the disorder, one copy from each parent.

Individuals with only one copy of a gene that causes ML are called carriers. They usually do not have symptoms of ML. The offspring of two carriers of an ML gene have a 25% chance of inheriting both genes and developing ML.

Demographics

MLs are very rare disorders that often have been misdiagnosed. Thus, the frequency of ML is not clear. However, since MLs are recessive disorders that only develop when both parents are carriers of one of the ML genes, the condition most often occurs in the offspring of closely-related individuals, such as first cousins. These disorders are much more prevalent in small, isolated populations. For example, among French-Canadians in one region of Quebec province, it is estimated that one out of every 39 people carries a gene for ML II and one out of 6,184 infants has the disorder. In contrast, over a 10-year-period, only 35 infants with ML II or ML III were born in Great Britain.

Although ML IV can occur in any nationality or ethnic group, more than 80% of all known cases are Jews of Eastern European descent (Ashkenazim). It is estimated that one out of 50 individuals of Ashkenazi descent is a carrier of ML IV. Worldwide, there are about 100 known cases of the disorder. However, it is thought that there are many more undiagnosed or misdiagnosed cases.

Signs and symptoms

The symptoms and the age of onset of ML II vary greatly, even within families. Some signs of ML II can be congenital, or present at birth. These may include:

- Multiple abnormalities in bone formation, particularly in the hip
- Limited mobility of the joints
- Multiple abnormalities of the skull and face
- A fold of skin extending from the inner corner of the eyelid, called an epicanthal fold

ML II and ML III are progressive conditions. Infants may show few symptoms of the disorder until lipids begin to accumulate and damage cells. Additional symptoms of ML II may include:

- Dwarfism
- Delayed mental and physical development
- Hearing loss
- Heart disease in the aortic valve
- Swollen liver and spleen

The symptoms of ML III are similar to those of ML II, but usually less severe. Additional signs of ML III may include:

- Acne
- Clouding of the cornea, the clear portion of the eye through which light passes
- Enlarged tongue

ML IV is characterized by mental and physical retardation and eye disorders. Many individuals with ML IV do not develop beyond the skill level of a one-year-old. However, some individuals with ML IV have very mild symptoms.

Infants with ML IV appear normal at birth. However signs of the disorder usually become apparent during the first year. Often, clouding or opacity of the cornea is the first symptom and vision problems may develop before the age of one. The physical and mental retardation may be mild at first, but often becomes severe as the disorder slowly progresses. Most individuals with ML IV never walk. Other signs of ML IV may include:

- Delayed growth
- Poor muscle tone
- Crossed eyes
- Puffy eyelids
- Aversion to light
- Degeneration of the retina, eventually leading to blindness

Diagnosis

ML II and ML III may be diagnosed by high levels of lysosomal enzymes, called hydrolases, in the blood. The absence of mucopolysaccharides in the urine indicates that the disorder is not a mucopolysaccharidosis. The microscopic examination of various cells reveals inclusion bodies. X rays are used to detect skeletal abnormalities.

The initial diagnosis of ML IV usually results from a biopsy. A small piece from the skin or from the membrane underneath the eyelid is removed and examined under a microscope for the accumulation of lipids and mucopolysaccharides in storage bodies.

Treatment and management

There is no cure for ML. Management of symptoms, close medical monitoring, and supportive care are the primary treatments.

Surgery can remove the thin layer of cells that causes the corneal cloudiness that is characteristic of ML IV. However, the layer of cells will grow back. Physical, occupational, and speech therapy can improve the functioning of children with ML IV.

Prognosis

The life expectancy for individuals with ML is not known.

Resources

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ORGANIZATIONS

Canadian Society for Mucopolysaccharide and Related Diseases. PO Box 64714, Unionville, ONT L3R OM9. Canada (905) 479-8701 or (800) 667-1846. <http://www.mpssociety.ca>.

Mucolipidosis IV Foundation. 719 East 17th St., Brooklyn, NY 11230. (718) 434-5067. <http://www.ML4.org>.

National Foundation for Jewish Genetic Diseases, Inc. 250 Park Ave., Suite 1000, New York, NY 10017. (212) 371-1030. <http://www.nfjgd.org>.

National MPS Society. 102 Aspen Dr., Downingtown, PA 19335. (610) 942-0100. Fax: (610) 942-7188. info @mpssociety.org. <http://www.mpssociety.org>.

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Margaret Alic, PhD

Mucopolysaccharidosis (MPS) type I *see* **Hurler syndrome**

Mucopolysaccharidosis II *see* **Hunter syndrome**

Mucopolysaccharidoses

Definition

Mucopolysaccharidosis (MPS) is a general term for a number of inherited diseases that are caused by the accumulation of mucopolysaccharides, resulting in problems with an individual's development. With each condition, mucopolysaccharides accumulate in the cells and tissues of the body because of a deficiency of a specific enzyme. The specific enzyme that is deficient or absent is what distinguishes one type of MPS from another. However, before these enzymes were identified, the MPS disorders were diagnosed by the signs and symptoms that an individual expressed. The discovery of these enzymes resulted in a reclassification of some of the MPS disorders. These conditions are often referred to as MPS I, MPS II, MPS III, MPS IV, MPS VI, MPS VII, and MPS IX. However, these conditions are also referred to by their original names, which are Hurler, Hurler-Scheie, Scheie (all MPS I), Hunter (MPS II), Sanfilippo (MPS III), Morquio (MPS IV), Maroteaux-Lamy (MPS VI), Sly (MPS VII), and Hyaluronidase deficiency (MPS IX).

Description

Mucopolysaccharides are long chains of sugar molecules that are essential for building the bones, cartilage, skin, tendons, and other tissues in the body. Normally, the human body continuously breaks down and builds mucopolysaccharides. Another name for mucopolysaccharides is glycosaminoglycans (GAGs). There are many different types of GAGs and specific GAGs are unable to be broken down in each of the MPS conditions. There are several enzymes involved in breaking down each GAG and a deficiency or absence of any of the essential enzymes can cause the GAG to not be broken down completely and results in its accumulation in the tissues and organs in the body. In some MPS conditions, in addition to the GAG being stored in the body, some of the incompletely broken down GAGs can leave the body via the urine. When too much GAG is stored, organs and tissues can be damaged or not function properly.

Genetic profile

Except for MPS II, the MPS conditions are inherited in an autosomal recessive manner. MPS conditions occur when both of an individual's genes that produce the specific enzyme contain a mutation, causing them to not work properly. When both genes do not work properly, either none or a reduced amount of the enzyme is produced. An individual with an autosomal recessive condition inherits one non-working gene from each parent. These parents are called "carriers" of the condition. When two people are known carriers for an autosomal recessive condition, they have a 25% chance with each pregnancy to have a child affected with the disease. Some individuals with MPS do have children of their own. Children of parents who have an autosomal recessive condition are all carriers of that condition. These children are not at risk to develop the condition unless the other parent is a carrier or affected with the same autosomal recessive condition.

Unlike the other MPS conditions, MPS II is inherited in an X-linked recessive manner. This means that the **gene** causing the condition is located on the X chromosome, one of the two sex **chromosomes**. Since a male has only one X chromosome, he will have the disease if the X chromosome inherited from his mother carries the defective gene. Females will be carriers of the condition if only one of their two X chromosomes has the gene that causes the condition.

Causes and symptoms

Each type of MPS is caused by a deficiency of one of the enzymes involved in breaking down GAGs. It is the accumulation of the GAGs in the tissues and organs in the body that cause the wide array of symptoms characteristic of the MPS conditions. The accumulating material is stored in cellular structures called lysosomes, and these disorders are also known as lysosomal storage diseases.

MPS I

MPS I is caused by a deficiency of the enzyme alpha-L-iduronidase. Three conditions, Hurler, Hurler-Scheie, and Scheie syndromes, are all caused by a deficiency of this enzyme. Initially, these three conditions were believed to be separate because each was associated with different physical symptoms and prognoses. However, once the underlying cause of these conditions was identified, it was realized that these three conditions were all variants of the same disorder. The gene involved with MPS I is located on chromosome 4p16.3.

MPS I H (HURLER SYNDROME) It has been estimated that approximately one baby in 100,000 will be born with **Hurler syndrome**. Individuals with Hurler syndrome tend to have the most severe form of MPS I. Symptoms of Hurler syndrome are often evident within the first year or two after birth. These infants often begin to develop as expected, but then reach a point where they begin to loose the skills that they have learned. Many of these infants may initially grow faster than expected, but their growth slows and typically stops by age three. Facial features also begin to appear "coarse." They develop a short nose, flatter face, thicker skin, and a protruding tongue. Additionally, their heads become larger and they develop more hair on their bodies with the hair becoming coarser. Their bones are also affected, with these children usually developing joint contractures (stiff joints), kyphosis (a "hunchback" curve of the spine), and broad hands with short fingers. Many of these children experience breathing difficulties, and respiratory infections are common. Other common problems include heart valve dysfunction, thickening of the heart muscle (cardiomyopathy), enlarged spleen and liver, clouding of the cornea, hearing loss, and carpal tunnel syndrome. These children typically do not live past age 12.

MPS I H/S (HURLER-SCHEIE SYNDROME) Hurler-Scheie syndrome is felt to be the intermediate form of MPS I, meaning that the symptoms are not as severe as those in individuals who have MPS I H but not as mild as those in MPS I S. Approximately one baby in 115,000 will be born with Hurler-Scheie syndrome. These individuals tend to be shorter than expected, and they can have normal intelligence, however, some individuals with MPS I H/S will experience learning difficulties. These individuals may develop some of the same physical features as those with Hurler syndrome, but usually they are not as severe. The prognosis for children with MPS I H/S is variable with some individuals dying during childhood, while others living to adulthood.

MPS I S (SCHEIE SYNDROME) Scheie syndrome is considered the mild form of MPS I. It is estimated that approximately one baby in 500,000 will be born with Scheie syndrome. Individuals with MPS I S usually have normal intelligence, but there have been some reports of individuals with MPS I S developing psychiatric problems. Common physical problems include corneal clouding, heart abnormalities, and orthopedic difficulties involving their hands and back. Individuals with MPS I S do not develop the facial features seen with MPS I H and usually these individuals have a normal life span.

MPS II (Hunter syndrome)

Hunter syndrome is caused by a deficiency of the enzyme iduronate-2-sulphatase. All individuals with Hunter syndrome are male, because the gene that causes the condition is located on the X chromosome, specifically Xq28. Like many MPS conditions, Hunter syndrome is divided into two groups, mild and severe. It has been estimated that approximately one in 110,000 males are born with Hunter syndrome, with the severe form being three times more common than the mild form. The severe form is felt to be associated with progressive mental retardation and physical disability, with most individuals dying before age 15. In the milder form, most of these individuals live to adulthood and have normal intelligence or only mild mental impairments. Males with the mild form of Hunter syndrome develop physical differences similar to males with the severe form, but not as quickly. Men with mild Hunter syndrome can have a normal life span and some have had children. Most males with Hunter syndrome develop joint stiffness, chronic diarrhea, enlarged liver and spleen, heart valve problems, hearing loss, kyphosis, and tend to be shorter than expected. These symptoms tend to progress at a different rate depending on if an individual has the mild or severe form of MPS II.

MPS III (Sanfilippo syndrome)

MPS III, like the other MPS conditions, was initially diagnosed by the individual having certain physical characteristics. It was later discovered that the physical symptoms associated with Sanfilippo syndrome could be caused by a deficiency in one of four enzymes. Each type of MPS III is now subdivided into four groups, labeled A-D, based on the specific enzyme that is deficient. All four of these enzymes are involved in breaking down the same GAG, heparan sulfate. Heparan sulfate is mainly found in the central nervous system and accumulates in the brain when it cannot be broken down because one of those four enzymes are deficient or missing.

MPS III is a variable condition with symptoms beginning to appear between ages two and six years of age. Because of the accumulation of heparan sulfate in the central nervous system, the central nervous system is severely affected. In MPS III, signs that the central nervous system is degenerating are usually evident in most individuals between ages six and 10. Many children with MPS III will develop seizures, sleeplessness, thicker skin, joint contractures, enlarged tongues, cardiomyopathy, behavior problems, and mental retardation. The life expectancy in MPS III is also variable. On average, individuals with MPS III live until they are teenagers, with some living longer and others not that long.

KEY TERMS

Cardiomyopathy—A thickening of the heart muscle.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Joint contractures—Stiffness of the joints that prevents full extension.

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mucopolysaccharide—A complex molecule made of smaller sugar molecules strung together to form a chain. Found in mucous secretions and intercellular spaces.

Recessive gene—A type of gene that is not expressed as a trait unless inherited by both parents.

X-linked gene—A gene carried on the X chromosome, one of the two sex chromosomes.

MPS IIIA (SANFILIPPO SYNDROME TYPE A) MPS IIIA is caused by a deficiency of the enzyme heparan N-sulfatase. Type IIIA is felt to be the most severe of the four types, in which symptoms appear and death occurs at an earlier age. A study in British Columbia estimated that one in 324,617 live births are born with MPS IIIA. MPS IIIA is the most common of the four types in Northwestern Europe. The gene that causes MPS IIIA is located on the long arm of chromosome 17 (location 17q25).

MPS IIIB (SANFILIPPO SYNDROME TYPE B) MPS IIIB is due to a deficiency in N-acetyl-alpha-D-glucosaminidase (NAG). This type of MPS III is not felt to be as severe as Type IIIA and the characteristics vary. Type IIIB is the most common of the four in southeastern Europe. The gene associated with MPS IIIB is also located on the long arm of chromosome 17 (location 17q21).

MPS IIIC (SANFILIPPO SYNDROME TYPE C) A deficiency in the enzyme acetyl-CoA-alpha-glucosaminide acetyltransferase causes MPS IIIC. This is considered a rare form of MPS III. The gene involved in MPS IIIC is believed to be located on chromosome 14.

MPS IIID (SANFILIPPO SYNDROME TYPE D) MPS IIID is caused by a deficiency in the enzyme N-acetylglucosamine-6-sulfatase. This form of MPS III is also rare. The gene involved in MPS IIID is located on the long arm of chromosome 12 (location 12q14).

MPS IV (Morquio syndrome)

As with several of the MPS disorders, Morquio syndrome was diagnosed by the presence of particular signs and symptoms. However, it is now known that the deficiency of two different enzymes can cause the characteristics of MPS IV. These two types of MPS IV are called MPS IV A and MPS IV B. MPS IV is also variable in its severity. The intelligence of individuals with MPS IV is often completely normal. In individuals with a severe form, skeletal abnormalities can be extreme and include dwarfism, kyphosis (outward-curved spine), prominent breastbone, flat feet, and knock-knees. One of the earliest symptoms seen in this condition usually is a difference in the way the child walks. In individuals with a mild form of MPS IV, limb stiffness and joint pain are the primary symptoms. MPS IV is one of the rarest MPS disorders, with approximately one baby in 300,000 born with this condition.

MPS IV A (MORQUIO SYNDROME TYPE A) MPS IV A is the "classic" or the severe form of the condition and is caused by a deficiency in the enzyme galactosamine-6-sulphatase. The gene involved with MPS IV A is located on the long arm of chromosome 16 (location 16q24.3).

MPS IV B (MORQUIO SYNDROME TYPE B) MPS IV B is considered the milder form of the condition. The enzyme, beta-galactosidase, is deficient in MPS IV B. The location of the gene that produces beta-galactosidase is located on the short arm of chromosome 3 (location 3p21).

MPS VI (Maroteaux-Lamy syndrome)

MPS VI, which is another rare form of MPS, is caused by a deficiency of the enzyme N-acetylglucosamine-4-sulphatase. This condition is also variable; individuals may have a mild or severe form of the condition. Typically, the nervous system or intelligence of an individual with MPS VI is not affected. Individuals with a more severe form of MPS VI can have airway obstruction, develop **hydrocephalus** (extra fluid accumulating in the brain) and have bone changes. Additionally, individuals with a severe form of MPS VI are more likely to die while in their teens. With a milder form of the condition, individuals tend to be shorter than expected for their age, develop corneal clouding, and live longer. The gene involved in MPS VI is believed to be located on the long arm of chromosome 5 (approximate location 5q11-13).

MPS VII (Sly syndrome)

MPS VII is an extremely rare form of MPS and is caused by a deficiency of the enzyme beta-glucuronidase. It is also highly variable, but symptoms are generally similar to those seen in individuals with Hurler syndrome. The gene that causes MPS VII is located on the long arm of chromosome 7 (location 7q21).

MPS IX (Hyaluronidase deficiency)

MPS IX is a condition that was first described in 1996 and has been grouped with the other MPS conditions by some researchers. MPS IX is caused by the deficiency of the enzyme hyaluronidase. In the few individuals described with this condition, the symptoms are variable, but some develop soft-tissue masses (growths under the skin). Also, these individuals are shorter than expected for their age. The gene involved in MPS IX is believed to be located on the short arm of chromosome 3 (possibly 3p21.3-21.2)

Many individuals with an MPS condition have problems with airway constriction. This constriction may be so serious as to create significant difficulties in administering general anesthesia. Therefore, it is recommended that surgical procedures be performed under local anesthesia whenever possible.

Diagnosis

While a diagnosis for each type of MPS can be made on the basis of the physical signs described above, several of the conditions have similar features. Therefore, enzyme analysis is used to determine the specific MPS disorder. Enzyme analysis usually cannot accurately determine if an individual is a carrier for a MPS condition. This is because the enzyme levels in individuals who are not carriers overlaps the enzyme levels seen in those individuals who are carrier for a MPS. With many of the MPS conditions, several mutations have been found in each gene involved that can cause symptoms of each condition. If the specific mutation is known in a family, **DNA** analysis may be possible.

Once a couple has had a child with an MPS condition, prenatal diagnosis is available to them to help determine if a fetus is affected with the same MPS as their other child. This can be accomplished through testing samples using procedures such as an **amniocentesis** or chorionic villus sampling (CVS). Each of these procedures has its own risks, benefits, and limitations.

Treatment

There is no cure for mucopolysaccharidosis, however, several types of experimental therapies are being

investigated. Typically, treatment involves trying to relieve some of the symptoms. For MPS I and VI, bone marrow transplantation has been attempted as a treatment option. In those conditions, bone marrow transplantation has sometimes been found to help slow down the progression or reverse some of symptoms of the disorder in some children. The benefits of a bone marrow transplantation are more likely to be noticed when performed on children under two years of age. However, it is not certain that a bone marrow transplant can prevent further damage to certain organs and tissues, including the brain. Furthermore, bone marrow transplantation is not felt to be helpful in some MPS disorders and there are risks, benefits, and limitations with this procedure. In 2000, ten individuals with MPS I received recombinant human alpha-L-iduronidase every week for one year. Those individuals showed an improvement with some of their symptoms. Additionally, there is ongoing research involving gene replacement therapy (the insertion of normal copies of a gene into the cells of patients whose gene copies are defective).

Prevention

No specific preventive measures are available for genetic diseases of this type. For some of the MPS diseases, biochemical tests are available that will identify healthy individuals who are carriers of the defective gene, allowing them to make informed reproductive decisions. There is also the availability of prenatal diagnosis for all MPS disease to detect affected fetuses.

Resources

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ORGANIZATIONS

Canadian Society for Mucopolysaccharide and Related Diseases. PO Box 64714, Unionville, ONT L3R-OM9. Canada (905) 479-8701 or (800) 667-1846. <http://www.mpssociety.ca>.

Children Living with Inherited Metabolic Diseases. The Quadrangle, Crewe Hall, Weston Rd., Crewe, Cheshire, CW1-6UR. UK 127 025 0221. Fax: 0870-7700-327. <http://www.climb.org.uk>.

Metabolic Information Network. PO Box 670847, Dallas, TX 75367-0847. (214) 696-2188 or (800) 945-2188.

National MPS Society. 102 Aspen Dr., Downingtown, PA 19335. (610) 942-0100. Fax: (610) 942-7188. info@mpssociety.org. <http://www.mpssociety.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Society for Mucopolysaccharide Diseases. 46 Woodside Rd., Amersham, Buckinghamshire, HP6 6AJ. UK +44 (01494) 434156. <http://www.mpssociety.co.uk>.

Zain Hansen MPS Foundation. 23400 Henderson Rd., Covelo, CA 95420. (800) 767-3121.

WEBSITES

National Library of Medicine. National Institutes of Health. <http://www.nlm.nih.gov/>

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Sharon A. Aufox, MS, CGC

Mucoxiscidosis *see* **Cystic fibrosis**

Muir-Torre syndrome

Definition

A syndrome is a condition in which a certain set of features is regularly seen. In Muir-Torre syndrome, the consistent features are skin tumors (sebaceous neoplasms) and internal organ cancers, most commonly colon cancer.

Description

Muir-Torre syndrome is named for two authors who provided some of the earliest descriptions of the condition, Muir in 1967 and Torre in 1968. Originally thought to be separate conditions, it is now known that Muir-Torre syndrome and Hereditary non-polyposis colon can-

KEY TERMS

Allelic—Related to the same gene.

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Colectomy—Surgical removal of the colon.

Colonoscopy—Procedure for viewing the large intestine (colon) by inserting an illuminated tube into the rectum and guiding it up the large intestine.

Colorectal—Of the colon and/or rectum.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genitourinary—Related to the reproductive and urinary systems of the body.

Hereditary non-polyposis colon cancer (HNPCC)—A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called Lynch syndrome.

hMLH1 and hMSH2—Genes known to control mismatch repair of genes.

Keratoacanthoma—A firm nodule on the skin typically found in areas of sun exposure.

Lymph node—A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

Lynch syndrome—A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called hereditary non-polyposis colon cancer (HNPCC).

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

Mismatch repair—Repair of gene alterations due to mismatching.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Radiation—High energy rays used in cancer treatment to kill or shrink cancer cells.

Sebaceous—Related to the glands of the skin that produce an oily substance.

Splenic flexure—The area of the large intestine at which the transverse colon meets the descending colon.

cer (HNPCC), also known as Lynch syndrome, are due to alterations in the same genes. Some of the features of the conditions are the same including increased risk of colorectal cancer (cancer of the colon and rectum) and cancer of other organs. Both conditions are hereditary cancer predisposition syndromes meaning that the risk of cancer has been linked to an inherited tendency for the disease. A unique feature of Muir-Torre syndrome is the skin tumors. The most common skin tumors associated with Muir-Torre syndrome are benign (non-cancerous) or malignant (cancerous) tumors of the oil-secreting (sebaceous) glands of the skin. Another relatively common skin finding is the presence of growths called keratoacanthomas.

Genetic profile

HNPCC and Muir-Torre syndrome are allelic meaning that these disorders are due to changes in the same genes. Genes, the units of instruction for the body, can have changes or mutations that develop over time. Certain mutations are repaired by a class of genes known as mismatch repair genes. When these genes are not functioning properly, there is a higher chance of cancer due to the alterations that accumulate in the genetic material. Heritable mutations in at least five mismatch repair genes have been linked to HNPCC although the majority, over 90%, are in the hMLH1 and hMSH2 genes. Mutations in hMLH1 and hMSH2 also have been reported in Muir-Torre syndrome, although most have been hMSH2 mutations. The location of the hMLH1 **gene** is on chromosome 3 at 3p21.3, while the location of hMSH2 is chromosome 2, 2p22-p21. **Genetic testing** for hMLH1 and hMSH2 is available but the detection rate for mismatch repair gene mutations is less than 100%. Therefore, diagnosis of Muir-Torre syndrome is not based on genetic testing alone but also on the presence of the typical features of the disease.

Muir-Torre syndrome is inherited in an autosomal dominant fashion. Thus, both men and women can have Muir-Torre syndrome and only one gene of the paired genes, needs to be altered to have the syndrome. Children

TABLE 1

Screening recommendations for patients with Muir-Torrie syndrome

Test/Procedure	Age	Frequency
Physical exam	20+	Every 3 years
	40+	Annually
Digital rectal exam	Any	Annually
Gualac of stool for occult blood	Any	Annually
Lab work-up	Any	
Carcinoembryonic antigen		
Complete blood cell count with differential and platelet count		
Erythrocyte sedimentation rate		
Serum chemistries (SMA-20)		
Urinalysis	Any	Annually
Chest roentgenogram	Any	Every 3–5 years
Colonoscopy	Any	Every 5 years
	If positive for polyps	Every 3 years

TABLE 2

Additional screening recommendations for females with Muir-Torrie syndrome

Test/Procedure	Age	Frequency
Breast exam	20–40	Every 3 years
	40+	Annually
Pelvic exam	18+ or sexually active	Annually
Pap smear	18+ or sexually active	Annually
Mammogram	40–49	Every 1–2 years
	50+	Annually
Endometrial biopsy	Menopause	Every 3–5 years after onset

of individuals with Muir-Torre syndrome have a one in two or 50% chance of inheriting the gene alteration. However, the symptoms of the syndrome are variable and not all individuals with the condition will develop all of the features.

Demographics

At least 250 cases of Muir-Torre syndrome, specifically, have been reported. It is estimated that between one in 200 to one in 2,000 people in Western countries carry an alteration in the genes associated with HNPCC but the rate of Muir-Torre syndrome itself has not been clarified. More males than females appear to exhibit the features of Muir-Torre syndrome. The average age at time of diagnosis of the syndrome is around 55 years.

Signs and symptoms

Skin findings

Sebaceous neoplasms typically appear as yellowish bumps on the skin of the head or neck but can be found on the trunk and other areas. The classification of the different types of sebaceous neoplasms can be difficult so microscopic evaluation is usually required for the final diagnosis. Keratoacanthomas are skin-colored or reddish, firm skin nodules that are distinct from sebaceous neoplasms upon microscopic examination. The skin findings in Muir-Torre syndrome can either appear before, during, or after the development of the internal cancer.

Internal findings

Internal organ cancers are common in Muir-Torre syndrome. Several individuals with Muir-Torre syndrome with multiple types of internal cancers have been reported. The most common internal organ cancer is colorectal cancer. Unlike colon cancers in the general population, the tumors due to Muir-Torre syndrome are more frequently seen around or closer to the right side of an area of the colon known as the splenic flexure. This tumor location, the meeting point of the transverse and the descending colon, is different than the usual location of colon cancer in the general population. Colon polyps, benign growths with the possibility of cancer development, have been reported in individuals with Muir-Torre syndrome; however, the number of polyps typically is limited.

Symptoms of colorectal cancer or polyps may include:

- red blood in stool
- weight loss
- pain or bloating in abdomen
- long-term constipation
- diarrhea
- decrease in stool size

The next most frequent cancer occurances in Muir-Torre syndrome are those of the genitourinary system, including uterine cancer, ovarian cancer, and bladder cancer. Other cancers that have been seen with Muir-Torre syndrome include breast cancers, blood cancers, head and neck cancers, and cancers of the small intestine.

Diagnosis

Since not all families with the features of Muir-Torre syndrome have identifiable mismatch repair gene alterations, diagnosis is based mainly on the presence of the physical features of the disease. Muir-Torre syndrome is defined by the presence of certain types of sebaceous neoplasms (sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas and keratoacanthomas with sebaceous differentiation) and at least one internal

organ cancer in the same individual. Muir-Torre syndrome may also be diagnosed if an individual has multiple keratoacanthomas, multiple internal organ cancers, and a family history of Muir-Torre syndrome. Testing of the hMLH1 and hMSH2 genes is available and could be done to confirm a diagnosis or to assist in testing at-risk relatives prior to development of symptoms. Given the complexity of this disorder, **genetic counseling** may be considered before testing.

Screening recommendations have been proposed for individuals with Muir-Torre or at-risk relatives. In addition to regular screening for the skin findings, screening for internal cancers may be considered. The effectiveness of screening for individuals with or at risk for Muir-Torre syndrome has yet to be proven.

Treatment and management

While it is not possible to cure the genetic abnormality that results in Muir-Torre syndrome, it is possible to prevent and treat the symptoms of the syndrome. The skin tumors are removed by freezing or cutting. If lymph nodes, small bean-sized lumps of tissue that are part of the immune system, are involved, these must be removed also. Radiation, high energy rays, to the affected area can be beneficial. A medication, isotretinoin, may reduce the risk of skin tumors. Internal organ cancers are treated in the standard manner, removal by surgery and possible treatment with radiation or cancer-killing medication (chemotherapy). Removal of the colon, colectomy, before colon cancer develops is an option with HNPCC and may be considered for individuals with Muir-Torre syndrome.

Prognosis

The cancers associated wth Muir-Torre syndrome are usually diagnosed at earlier ages than typically seen. For instance, the average age at diagnosis of colorectal cancer is 10 years earlier than in the general population. Fortunately, the internal organ cancers seen in Muir-Torre syndrome appear less aggressive. So, the prognosis may be better for a person with colon cancer due to Muir-Torre syndrome than colon cancer in the general population.

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American Cancer Society. 1599 Clifton Road NE, Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda, MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

WEBSITES

M.D. Anderson Cancer Center. <http://www3.mdanderson.org/depts/hcc>.

Kristin Baker Niendorf, MS, CGC

Multifactorial inheritance

Definition

Many common congenital malformations and diseases are caused by a combination of genetic and environmental factors. The term multifactorial inheritance is used to describe conditions that occur due to these multiple factors. In contrast to dominantly or recessively inherited diseases, multifactorial traits do not follow any particular pattern of inheritance in families. Multifactorial conditions do tend to cluster in families, but **pedigree analysis** does not reveal a specific pattern of affected individuals. Some multifactorial conditions occur because of the interplay of many genetic factors and limited environmental factors. Others occur because of limited genetic factors and significant environmental factors. The number of genetic and environmental factors vary, as does the amount of impact of each factor on the presence or severity of disease. Often there are multiple susceptibility genes involved, each of which has an additive affect on outcome.

Examples of congenital malformations following a multifactorial pattern of inheritance include **cleft lip and palate**, neural tube defects, and heart defects. Adult onset diseases that follow multifactorial inheritance include diabetes, heart disease, **epilepsy** and affective disorders like **schizophrenia**. Many normal traits in the general population follow multifactorial inheritance. For instance, height, intelligence, and blood pressure are all determined in part by genetic factors, but are influenced by environmental factors.

Continuous and discontinuous traits

Some multifactorial traits are considered continuous because there is bell shaped distribution of those traits in the population. These are quantitative traits such as height. Other traits are discontinuous because there is a cutoff or threshold of genetic and environmental risk that

must be crossed in order for the trait to occur. An example would be a malformation like a cleft lip, in which the person is either affected or unaffected. In both cases, the genetic and environmental factors that are involved in the occurrence of the condition are referred to as liability.

Pyloric stenosis

An example of a discontinuous multifactorial trait that follows the threshold model is **pyloric stenosis**. Pyloric stenosis is a narrowing of the pylorus, the connection between the stomach and the intestine. Symptoms of pyloric stenosis include vomiting, constipation, and weight loss. Surgery is often needed for repair. An important genetic factor in the occurrence of pyloric stenosis is a person's sex. The condition is five times more common in males. The liability is higher in women, such that more or stronger genetic and environmental factors are needed to cause the condition in women. Therefore, male first-degree relatives of a female who is affected with pyloric stenosis have a higher risk to be born with the condition than do female first-degree relatives of the same person. This is because the stronger genetic factors present in the family (represented by the affected female) are more likely to cross the lower liability threshold in male family members.

Recurrence risks

Recurrence risks for multifactorial traits are based on empiric data, or observations from other families with affected individuals. Most multifactorial traits have a recurrence risk to first-degree relatives of 2-5%. However, empiric data for a specific condition may provide a more specific recurrence risk. Some general characteristics about the recurrence risk of multifactorial traits include:

- The recurrence risk to first-degree relatives is increased above the general population risk for the trait, but the risk drops off quickly for more distantly related individuals.
- The recurrence risk increases proportionately to the number of affected individuals in the family. A person with two affected relatives has a higher risk than someone with one affected relative.
- The recurrence risk is higher if the disorder is in the severe range of the possible outcomes. For instance, the risk to a relative of a person with a unilateral cleft lip is lower than if the affected person had bilateral cleft lip and a cleft palate.
- If the condition is more common in one sex, the recurrence risk for relatives is higher in the less affected sex. Pyloric stenosis is an example of this.
- Recurrence risks quoted are averages and the true risk in a specific family may be higher or lower.

It is also important to understand that recurrence risks for conditions may vary from one population to another. For instance, North Carolina, South Carolina, and Texas all have a higher incidence of neural tube defects that other states in the United States. Ireland has a higher incidence of neural tube defects than many other countries.

KEY TERMS

Candidate gene—A gene that encodes proteins believed to be involved in a particular disease process.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Loci—The physical location of a gene on a chromosome.

Phenotype—The physical expression of an individuals genes.

Polymorphism—A change in the base pair sequence of DNA that may or may not be associated with a disease.

Examples of multifactorial traits

Neural tube defects

Neural tube defects are birth defects that result from the failure of part of the spinal column to close approximately 28 days after conception. If the anterior (top) portion of the neural tube fails to close, the most severe type of neural tube defect called **anencephaly** results. Anencephaly is the absence of portions of the skull and brain and is a lethal defect. If a lower area of the spine fails to close, **spina bifida** occurs. People with spina bifida have varying degrees of paralysis, difficulty with bowel and bladder control, and extra fluid in the brain called **hydrocephalus**. The size and location of the neural tube opening determines the severity of symptoms. Surgery is needed to cover or close the open area of the spine. When hydrocephalus is present, surgery is needed for shunt placement.

Neural tube defects are believed to follow a multifactorial pattern of inheritance. Empiric data suggests that the risk to first-degree relatives of a person with a neural tube defect is increased 3-5%. The risk to other more distantly related relatives decreases significantly. In

addition, it is known that a form of vitamin B called folic acid can significantly reduce the chance for the occurrence of a neural tube defect. Studies have shown that when folic acid is taken at least three months prior to pregnancy and through the first trimester, the chance for a neural tube defect can be reduced by 50-70%. This data suggests that one environmental factor in the occurrence of neural tube defects is maternal folate levels. However, some women who are not folate deficient have babies with open spine abnormalities. Other women who are folate deficient do not have babies with spinal openings. The exact interplay of genetic and environmental factors in the occurrence of neural tube defects is not yet clear. Studies are currently underway to identify genes involved in the occurrence of neural tube defects.

Diabetes

There are two general types of diabetes. Type I is the juvenile onset form that often begins in adolescence and requires insulin injections for control of blood sugar levels. Type II is the more common, later onset form that does not usually require insulin therapy. Both are known to be influenced by environmental factors and show familial clustering. Important environmental factors involved in the occurrence of diabetes include diet, viral exposure in childhood, and certain drug exposures. It is clear that genetic factors are involved in the occurrence of type I diabetes since empiric data show that 10% of people with the condition have an affected sibling. An important susceptibility **gene** for type I diabetes has been discovered on chromosome 6. The gene is called IDDM1. Another gene on chromosome 11 has also been identified as a susceptibility gene. Studies in mice have indicated that there are probably 12-20 susceptibility genes for insulin dependent diabetes. IDDM1 is believed to have a strong effect and is modified by other susceptibility genes and environmental factors.

Analysis of multifactorial conditions

Genetic studies of multifactorial traits are usually more difficult than genetic studies of dominant or recessive traits. This is because it is difficult to determine the amount of genetic contribution to the multifactorial trait versus the amount of environmental contribution. For most multifactorial traits, it is not possible to perform a genetic test and determine if a person will be affected. Instead, studies involving multifactorial traits strive to determine the proportion of the phenotype due to genetic factors and to identify those genetic factors. The inherited portion of a multifactorial trait is called heritability.

Disease association studies

One method of studying the heritability of multifactorial traits is to determine if a candidate gene is more common in an affected population than in the general population.

Sibling pair studies

Another type of study involves gathering many pairs of siblings who are affected with a multifactorial trait. Researchers try to identify polymorphisms common in the sibling pairs. These polymorphisms can then be further analyzed. They can also study candidate genes in these sibling pairs. Studying individuals who are at the extreme end of the affected range and are thought to have a larger heritability for the trait can strengthen this type of study.

Twin studies

Another approach is to study a trait of interest in twins. Identical twins have 100% of their genes in common. Non-identical twins have 50% of their genes in common, just like any other siblings. In multifactorial traits, identical twins will be concordant for the trait significantly more often than non-identical twins. One way to control for the influence of a similar environment on twins is to study twins who are raised separately. However, situations in which one or both identical twins were adopted out and are available for study are rare.

Linkage analysis and animal studies are also used to study the heritability of conditions, although there are significant limitations to these approaches for multifactorial traits.

Ethical concerns of testing

One of the goals of studying the genetic factors involved in multifactorial traits is to be able to counsel those at highest genetic risk about ways to alter their environment to minimize risk of symptoms. However, **genetic testing** for multifactorial traits is limited by the lack of understanding about how other genes and environment interact with major susceptibility genes to cause disease. Testing is also limited by genetic heterogeneity for major susceptibility loci. Often the attention of the media to certain genetic tests increases demand for the test, when the limitations of the test are not fully explained. Therefore, it is important for people to receive appropriate pre-test counseling before undergoing genetic testing. Patients should consider the emotional impact of both positive and negative test results. Patients should understand that insurance and employment discrimination might occur due to test results. In addition,

there may not be any treatment or lifestyle modification available for many multifactorial traits for which a genetic test is available. The patient should consider the inability to alter their risk when deciding about knowing their susceptibility for the condition. When a person chooses to have testing, it is important to have accurate post-test counseling about the result and its meaning.

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Sonja Rene Eubanks, MS

Multiple cartilaginous exostoses *see* **Hereditary multiple exostoses**

Multiple endocrine neoplasias

Definition

The multiple endocrine neoplasia (MEN) syndromes are four related disorders affecting the thyroid and other hormonal (endocrine) glands of the body. MEN has previously been known as familial endocrine adenomatosis.

The four related disorders are all neuroendocrine tumors. These tumorous cells have something in common, they produce hormones, or regulatory substances for the body's homeostasis. They come from the APUD (amine precursor and uptake decarboxylase) system, and have to do with the cell apparatus and function to make these substances common to the cell line. Neuroendocrine tumors cause syndromes associated with each other by genetic predisposition.

Description

The four forms of MEN are MEN1 (Wermer syndrome), MEN2A (Sipple syndrome), MEN2B (previously known as MEN3), and familial medullary thyroid carcinoma (FMTC). Each is an autosomal dominant genetic condition, and all except FMTC predisposes to hyperplasia (excessive growth of cells) and tumor formation in a number of endocrine glands. FMTC predisposes only to this type of thyroid cancer.

Individuals with MEN1 experience hyperplasia of the parathyroid glands and may develop tumors of several endocrine glands including the pancreas and pituitary. The most frequent symptom of MEN1 is hyperparathyroidism. Hyperparathyroidism results from overgrowth of the parathyroid glands leading to excessive secretion of parathyroid hormone, which in turn leads to elevated blood calcium levels (hypercalcemia), kidney stones, weakened bones, fatigue, and weakness. Almost all individuals with MEN1 show parathyroid symptoms by the age of 50 years with some individuals developing symptoms in childhood.

Tumors of the pancreas, called pancreatic islet cell carcinomas, may develop in individuals with MEN1. These tumors tend to be benign, meaning that they do not spread to other body parts. However, on occasion these tumors may become malignant or cancerous and thereby a risk of metastasis, or spreading, of the cancer to other body parts becomes a concern. The pancreatic tumors associated with MEN1 may be called non-functional tumors as they do not result in an increase in hormone production and consequently, no symptoms are produced. However, in some cases, extra hormone is produced by the tumor and this results in symptoms; the symptoms depend upon the hormone produced. These symptomatic tumors are referred to as functional tumors. The most common functional tumor is gastrinoma followed by insulinoma. Other less frequent functional tumors are VIPoma and glucagonoma. Gastrinoma results in excessive secretion of gastrin (a hormone secreted into the stomach to aid in digestion), which in turn may cause upper gastrointestinal ulcers; this condition is sometimes referred to as Zollinger-Ellison syndrome. About one in three people with MEN1 develop a gastrinoma. Insulinoma causes an increase in insulin levels, which in turn causes glucose levels to decrease. This tumor causes symptoms consistent with low glucose levels (hypoglycemia, low blood sugar) which include anxiety, confusion, tremor, and seizure during periods of fasting. About 40–70% of individuals with MEN1 develop a pancreatic tumor.

The pituitary may also be affected—the consequence being extra production of hormone. The most fre-

KEY TERMS

Bilateral—Relating to or affecting both sides of the body or both of a pair of organs.

Endocrine glands—A system of ductless glands that regulate and secrete hormones directly into the bloodstream.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Hyperplasia—An overgrowth of normal cells within an organ or tissue.

Medullary thyroid cancer (MTC)—A slow-growing tumor associated with MEN.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Multifocal—A pathological term meaning that instead of finding one tumor in the tissue multiple tumors are found.

Neoplasm—An abnormal growth of tissue; for example, a tumor.

Parathyroid glands—A pair of glands adjacent to the thyroid gland that primarily regulate blood calcium levels.

Pheochromocytoma—A small vascular tumor of the inner region of the adrenal gland. The tumor causes uncontrolled and irregular secretion of certain hormones.

Pituitary gland—A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Thyroid gland—A gland located in the front of the neck that is responsible for normal body growth and metabolism. The thyroid traps a nutrient called iodine and uses it to make thyroid hormones, which allow for the breakdown of nutrients needed for growth, development and body maintenance.

Ultrasound examination—Visualizing the unborn baby while it is still inside the uterus.

quently occurring pituitary tumor is prolactinoma, which results in extra prolactin (affects bone strength and fertility) being produced. Less commonly, the thymus and adrenal glands may also be affected and in rare cases, a tumor called a carcinoid may develop. Unlike MEN2, the thyroid gland is rarely involved in MEN1 symptoms.

Patients with MEN2A experience two main symptoms, medullary thyroid carcinoma (MTC) and a tumor of the adrenal gland known as pheochromocytoma. Medullary thyroid carcinoma is a slow-growing cancer that is preceded by a condition called C-cell hyperplasia. C-cells are a type of cell within the thyroid gland that produce a hormone called calcitonin. About 40–50% of individuals with MEN2A develop C-cell hyperplasia followed by MTC by the time they are 50 years old and 70% will have done so by the time they are 70 years old. In some cases, individuals develop C-cell hyperplasia and MTC in childhood. Medullary thyroid carcinoma tumors are often multifocal and bilateral.

Pheochromocytoma is usually a benign tumor that causes excessive secretion of adrenal hormones, which in turn can cause life-threatening hypertension (high blood pressure) and cardiac arrhythmia (abnormal heart beats). About 40% of people with MEN2A will develop a pheochromocytoma. Individuals with MEN2A also have a tendency for the parathyroid gland to increase in size (hypertrophy) as well as for tumors to develop in the parathyroid gland. It has been found that about 25–35% of individuals with MEN2A will develop parathyroid involvement.

Individuals with MEN2B also develop MTC and pheochromocytoma. However, the medullary thyroid carcinomas often develop at much younger ages, often before the age of one year, and they tend to be more aggressive tumors. About half of the individuals with MEN2B develop a pheochromocytoma with some cases being diagnosed in childhood. All individuals with MEN2B develop additional conditions, which make it distinct from MEN2A. These extra features include a characteristic facial appearance with swollen lips; tumors of the mucous membranes of the eye, mouth, tongue, and nasal cavity; enlarged colon; and skeletal abnormalities, such as long bones and problems with spinal curving. Hyperparathyroidism is not seen in MEN2B as it is in MEN2A. Unlike the other three MEN syndromes, individuals with MEN2B may not have a family history of MEN2B. In at least half of the cases and perhaps more, the condition is new in the individual affected.

Medullary thyroid carcinoma may also occur in families but family members do not develop the other

TABLE 1

Association of multiple endocrine neoplasias with other conditions

Form	Inheritance	Associated diseases/conditions	Affected gene
MEN 1 (Wermer syndrome)	Autosomal dominant	Parathyroid hyperplasia Pancreatic islet cell carcinomas Pituitary hyperplasia Thymus, adrenal, carcinoid tumors (less common)	MEN 1
MEN 2A (Sipple syndrome)	Autosomal dominant	Medullary thyroid carcinoma Pheochromocytoma Parathyroid hyperplasia	RET
MEN 2B	Autosomal dominant	Medullary thyroid carcinoma Pheochromocytoma Parathyroid hyperplasia Swollen lips Tumors of mucous membranes (eyes, mouth, tongue, nasal cavities) Enlarged colon Skeletal problems such as spinal curving	RET
Familial medullary thyroid carcinoma	Autosomal dominant	Medullary thyroid carcinoma	RET

endocrine conditions seen in MEN2A and MEN2B. This is referred to as familial medullary thyroid carcinoma (FMTC) and it is a subtype of MEN2. Familial medullary thyroid cancer is suggested when other family members have also developed MTC, if the tumor is bilateral, and/or if the tumor is multifocal. In comparison to MEN2A and MEN2B, individuals with FMTC tend to develop MTC at older ages and the disease appears to be more indolent or slow progressing.

About one fourth (25%) of MTC occurs in individuals who have MEN2A, MEN2B, and FMTC.

Genetic profile

All four MEN syndromes follow autosomal dominant **inheritance**, meaning that every individual diagnosed with a MEN syndrome has a 50% (1 in 2) chance of passing on the condition to each of his or her children. Additionally, both men and women may inherit and pass on the genetic mutation.

MEN1 results from alterations or mutations in the MEN1 **gene**. Nearly every individual inheriting the MEN1 gene alteration will develop hyperparathyroidism, although the age at which it is diagnosed may differ among family members. Individuals inheriting the familial mutation may also develop one of the other characteristic features of MEN1, however, this often differs among family members as well.

The three subtypes of MEN2 are caused by mutations in another gene known as RET. Every individual who inherits a RET mutation will develop MTC during his or her lifetime, although the age at the time of diagnosis is often different in each family member. Multiple different mutations have been identified in individuals and families that have MEN2A. Likewise, several different mutations have been identified in individuals and families with FMTC. An interesting finding has been that a few families that clearly have MEN2A and a few families that clearly have FMTC have the same mutation. The reason the families have developed different clinical features is not known. In contrast to MEN2A and FMTC, individuals with MEN2B have been found, in more than 90% of cases, to have the same RET mutation. This mutation is located in a part of the gene that has never been affected in individuals and families with MEN2A and FMTC.

Demographics

MEN syndromes are not common. It has been estimated that MEN1 occurs in 3–20 out of 100,000 people. The incidence of MEN2 has not been published, but it has been reported that MEN2B is about ten-fold less common than MEN2A. MEN syndromes affect both men and women and it occurs worldwide.

Signs and symptoms

General symptoms of the characteristic features of the MEN syndromes and their causes include:

- Hyperparathyroidism, which may or may not cause symptoms. Symptoms that occur are related to the high levels of calcium in the bloodstream such as kidney stones, fatigue, muscle or bone pain, indigestion, and constipation.
- Medullary thyroid carcinoma may cause diarrhea, flushing, and depression.
- Pheochromocytoma may cause a suddenly high blood pressure and headache, palpitations or pounding of the heart, a fast heart beat, excessive sweating without exer-

tion, and/or development of these symptoms after rising suddenly from bending over.

Diagnosis

Diagnosis of the MEN syndromes has in the past depended upon clinical features and laboratory test results. Now that the genes responsible for these conditions have been identified, **genetic testing** provides another means of diagnosing individuals and families with these conditions. However, all of these tumors have a higher incidence of sporadic cases. It is important to ask the patient about family members when one of these types of tumor is diagnosed.

MEN1 is typically diagnosed from clinical features and from testing for parathyroid hormone (PTH). An elevated PTH indicates that hyperparathyroidism is present. When an individual develops a MEN1 related symptom or tumor, a complete family history should also be taken. If no family history of MEN1 or related problems such as kidney stones and pepic ulcers exists and close family members, i.e. parents, siblings and children, have normal serum calcium levels, then the person unlikely has MEN1. However, if the individual is found to have a second symptom or tumor characteristic of MEN1, the family history is suggestive of MEN1, and/or close family members have increased serum calcium levels, then MEN1 may be the correct diagnosis.

As of 1998, genetic testing for the MEN1 gene has helped with evaluating individuals and families for MEN1. If an individual apparently affected by MEN1 is found to have a mutation in the MEN1 gene, then this positive test result confirms the diagnosis. However, as of 2001, genetic testing of the MEN1 gene does not identify all mutations causing MEN1; consequently, a negative test result does not remove or exclude the diagnosis.

MEN2A is typically diagnosed from clinical features and from laboratory testing of calcitonin levels. Elevated calcitonin levels indicate C-cell hyperplasia and/or MTC is present. When an individual develops a MEN2A related symptom or tumor, a complete family history should be taken. If no family history of related problems exists and close family members, i.e. parents, siblings, and children, have normal calcitonin levels, then the person unlikely has MEN2A. However, if the individual is found to have a second symptom or tumor characteristic of MEN2A, the family history is suggestive of MEN2A, and/or close family members have increased calcitonin levels, then MEN2A may be the correct diagnosis.

As of 1993, genetic testing for the RET gene has helped with evaluating an individual and/or family for MEN2A. If an individual apparently affected by MEN2A is found to have a mutation in the RET gene, then this positive test result confirms the diagnosis. However, as of 2001, genetic testing of the RET gene does not identify all mutations causing MEN2A and FMTC; consequently, a negative test result does not remove or exclude the diagnosis.

Diagnosis of MEN2B can be made by physical examination and a complete medical history.

Diagnosis of FMTC may be made when the family history includes four other family members having developed MTC with no family member having developed a pheochromocytoma or pituitary tumor. Genetic testing of the RET gene may also assist with diagnosis.

Genetic testing of the MEN1 gene and of the RET gene allows individuals to be diagnosed prior to the onset of symptoms; this is often called predictive genetic testing. It is important to note that individuals should not undergo predictive genetic testing prior to the identification of the familial genetic mutation. Genetic testing of a family member clinically affected by the condition needs to be done first in order to identify the familial mutation. If this is not done, a negative result in an asymptomatic individual may not be a true negative test result.

Prenatal diagnosis of unborn babies is now technically possible via **amniocentesis** or chorionic villus sampling (CVS). However, prior to undergoing these procedures, the familial mutation needs to have been identified. An additional issue in prenatal diagnosis is how the test result will be used with regard to continuation of the pregnancy. Individuals considering prenatal diagnosis of MEN1 or MEN2 should confirm its availability prior to conception.

Genetic testing is best done in consultation with a geneticist (a doctor specializing in genetics) and/or genetic counselor.

Treatment and management

No cure or comprehensive treatment is available for the MEN syndromes. However, some of the consequences of the MEN syndromes can be symptomatically treated and complications may be lessened or avoided by early identification.

For individuals affected by MEN1, hyperparathyroidism is often treated by surgery. The parathyroids may be partially or entirely removed. If they are entirely removed, the individual will need to take calcium and vitamin D supplements. The pancreatic tumors that develop may also be removed surgically or pharmacological treatment (medication) may be given to provide relief from symptoms. As of 2001, the treatment of pancreatic tumors remains controversial as the most effective treatment has not been identified. Pituitary tumors that

develop may not require treatment, but if so, medication has often been effective. Surgery and radiation are used in rare cases.

Children of a parent affected by MEN1 should begin regular medical screening in childhood. It has been suggested that children beginning at five to 10 years of age begin having annual measurements of serum calcium, serum prolactin, and of the pancreatic, pituitary, and parathyroid hormones. The child should also undergo radiographic imaging (ultrasound, MRI examination) of the pancreas and pituitary. If the family history includes family members developing symptoms of MEN1 at younger than usual ages, then the children will need to begin medical screening at a younger age as well.

For the three types of MEN2, the greatest concern is the development of medullary thyroid carcinoma. Medullary thyroid carcinoma can be detected by measuring levels of the thyroid hormone, calcitonin.

Treatment of MTC is by surgical removal of the thyroid and the neighboring lymph nodes, although doctors may disagree at what stage to remove the thyroid. After thyroidectomy, the patient will receive normal levels of thyroid hormone orally or by injection. Even when surgery is performed early, metastatic spread of the cancer may have already occurred. Since this cancer is slow growing, metastasis may not be obvious. Metastasis is very serious in MTC because chemotherapy and radiation therapy are not effective in controlling its spread.

In the past, children who had a parent affected by one of the MEN2 syndromes were screened for MTC by annual measurement of calcitonin levels. More recently, it has been determined that MTC can be prevented by prophylactic thyroidectomy, meaning that the thyroid gland is removed without it being obviously affected by cancer. As of 2001, it is not uncommon for a child as young as one year of age, when the family history is of MEN2B, or six years of age, when the family history is of MEN2A or FMTC, to undergo prophylactic thyroidectomy in order to prevent the occurrence of MTC.

Pheochromocytomas that occur in MEN2A and MEN2B can be cured by surgical removal of this slow growing tumor. Pheochromocytomas may be screened for using annual abdominal ultrasound or CT examination and laboratory testing.

For individuals diagnosed with MEN2, it is also recommended that the pituitary be screened by laboratory tests.

In general, each tumor may be approached surgically. However, problems occur when the tumors are multiple, when the whole gland is involved (hyperplasia as opposed to tumor), when replacement therapy is difficult (pituitary or adrenal), or when the gland makes multiple hormones (if the gland is removed, hormone replacement therapy becomes necessary).

Prognosis

Diagnosed early, the prognosis for the MEN conditions is reasonably good, even for MEN2B, the most dangerous of the four forms. Medullary thyroid cancer can be cured when identified early. The availability of genetic testing to identify family members at risk for developing the conditions will hopefully lead to earlier treatment and improved outcomes.

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Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202) 966-5557. Fax: (888) 394-3937 info@geneticalliance. <http://www.geneticalliance.org>.

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Cindy L. Hunter, MS, CGC

Multiple lentigenes syndrome

Definition

Multiple lentigenes syndrome is a rare genetic condition that causes the affected individual to have many dark brown or black freckle-like spots on the skin, as well as other symptoms.

Description

Multiple lentigenes syndrome is a genetic disorder that results in characteristic marking of the skin, abnormalities in the structure and function of the heart, hearing loss, wide-set eyes, and other symptoms. Other terms for multiple lentigenes syndrome include cardiomyopathic lentiginosis and LEOPARD syndrome. LEOPARD syndrome is an acronym for the seven most commonly observed symptoms of the disorder:

- (L)entigenes, or small dark brown and black spots on the skin;
- (E)lectrocardiographic conduction defects, or abnormalities of the muscle activity in the heart;
- (O)cular hypertelorism, or eyes that are spaced farther apart than normal;
- (P)ulmonary stenosis, or narrowing of the lower right ventricle of the heart;
- (A)bnormalities of the genitals, such as undescended testicles or missing ovaries;
- (R)etarded growth leading to shortness of stature;
- (D)eafness or hearing loss.

The lentigenes, or skin spots, observed in multiple lentigenes syndrome are similar in size and appearance to freckles, but unlike freckles, they are not affected by sun exposure.

Genetic profile

Multiple lentigenes syndrome is inherited as an autosomal dominant trait. Autosomal means that the syndrome is not carried on a sex chromosome, while dominant means that only one parent has to pass on the **gene mutation** in order for the child to be affected with the syndrome.

As of 2001, the specific gene mutation responsible for multiple lentigenes syndrome had not been identified.

KEY TERMS

Lentigene—A dark colored spot on the skin.

Stenosis—The constricting or narrowing of an opening or passageway.

Demographics

Multiple lentigenes syndrome is extremely rare. Due to the small number of reported cases, demographic trends for the disease have not been established. There does not seem to be any clear ethnic pattern to the disease. Both males and females appear to be affected with the same probability.

Signs and symptoms

The most characteristic symptom of the disease is the presence of many dark brown or black spots, ranging in size from barely visible to 5 cm in diameter, all over the face, neck, and chest. They may also be present on the arms and legs, genitalia, palms of the hands, and soles of the feet. The spots appear in infancy or early childhood and become more numerous until the age of puberty. There may also be lighter brown (café au lait) birthmarks on the skin.

Heart defects, such as the pulmonary stenosis and electrocardiographic conduction abnormalities described above, are another hallmark of multiple lentigenes syndrome. Other areas of narrowing (stenosis) in different areas of the heart may be present, as well as abnormalities in the atrial septum, the wall between the upper left and right chambers of the heart. There is an increased risk of heart disease and tumors of the heart.

In addition to the feature of widely spaced eyes, other facial abnormalities may include low-set or prominent ears, drooping eyelids, a short neck, or a projecting jaw. In some cases of multiple lentigenes syndrome, additional skeletal malformations have been reported, including a sunken breastbone, rib anomalies, curvature of the spine (**scoliosis**), and webbing of the fingers.

Deafness or hearing loss is observed in about 25% of the cases of multiple lentigenes syndrome. Some people affected with the syndrome also exhibit mild developmental delay. Other reported neurological findings include seizures, eye tics, and abnormal electrical activity in the brain.

People with multiple lentigenes syndrome often exhibit genital abnormalities such as undescended testicles or a small penis in men, or missing or underdeveloped ovaries in women. The onset of puberty may be

delayed or even absent. Affected individuals are usually under the twenty-fifth percentile in height, although their body weight is in the normal range.

Diagnosis

Diagnosis is usually made based on the observation of multiple lentigenes and the presence of two or more of the other symptoms that form the LEOPARD acronym. A family history is also helpful since the syndrome has dominant **inheritance**. There is currently no medical test that can definitively confirm the diagnosis of multiple lentigenes syndrome.

Treatment and management

Treatment is directed toward the specific conditions of the individual. For example, heart conditions can be managed with the use of a pacemaker and appropriate medications, as well as regular medical monitoring. Hearing loss may be improved with the use of hearing aids.

Genetic counseling is recommended when there is a family history of freckle-like spotting of the skin and heart defects, as these suggest the possibility of inherited multiple lentigenes syndrome.

Prognosis

The prognosis for people with multiple lentigenes syndrome is good provided that the appropriate care for any associated medical conditions is available.

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Paul A. Johnson

Muscular dystrophy

Definition

Muscular dystrophy is the name for a group of inherited disorders in which strength and muscle bulk gradually decline. Nine types of muscular dystrophies are generally recognized.

Description

The muscular dystrophies include:

- ***Duchenne muscular dystrophy*** *(DMD)*: DMD affects young boys, causing progressive muscle weakness, usually beginning in the legs. It is a severe form of muscular dystrophy. DMD occurs in about one in 3,500 male births, and affects approximately 8,000 boys and young men in the United States. A milder form occurs in a very small number of female carriers.
- *Becker muscular dystrophy (BMD)*: BMD affects older boys and young men, following a milder course than DMD. It occurs in about one in 30,000 male births.
- *Emery-Dreifuss muscular dystrophy (EDMD)*: EDMD affects both males and females because it can be inherited as an autosomal dominant or recessive disorder. Symptoms include contractures and weakness in the calves, weakness in the shoulders and upper arms, and problems in the way electrical impulses travel through the heart to make it beat (heart conduction defects). Fewer than 300 cases of EDMD have been reported in the medical literature.
- *Limb-girdle muscular dystrophy (LGMD)*: LGMD begins in late childhood to early adulthood and affects both men and women, causing weakness in the muscles around the hips and shoulders, and weakness in the limbs. It is the most variable of the muscular dystrophies, and there are several different forms of the condition now recognized. Many people with suspected LGMD have probably been misdiagnosed in the past, and therefore, the prevalence of the condition is difficult to estimate. The highest prevalence of LGMD is in a small mountainous Basque province in northern Spain, where the condition affects 69 persons per million.
- *Facioscapulohumeral muscular dystrophy (FSH)*: FSH, also known as Landouzy-Dejerine condition, begins in late childhood to early adulthood and affects both men and women, causing weakness in the muscles of the face, shoulders, and upper arms. The hips and legs may also be affected. FSH occurs in about one out of every 20,000 people, and affects approximately 13,000 people in the United States.

- ***Myotonic dystrophy***: Also known as Steinert's disease, it affects both men and women, causing generalized weakness first seen in the face, feet, and hands. It is accompanied by the inability to relax the affected muscles (myotonia). Symptoms may begin from birth through adulthood. It is the most common form of muscular dystrophy, affecting more than 30,000 people in the United States.
- *Oculopharyngeal muscular dystrophy (OPMD)*: OPMD affects adults of both sexes, causing weakness in the eye muscles and throat. It is most common among French Canadian families in Quebec, and in Spanish-American families in the southwestern United States.
- *Distal muscular dystrophy (DD)*: DD is a group of rare muscle diseases that have weakness and wasting of the distal (farthest from the center) muscles of the forearms, hands, lower legs, and feet in common. In general, the DDs are less severe, progress more slowly, and involve fewer muscles than the other dystrophies. DD usually begins in middle age or later, causing weakness in the muscles of the feet and hands. It is most common in Sweden, and rare in other parts of the world.
- *Congenital muscular dystrophy (CMD)*: CMD is a rare group of muscular dystrophies that have in common the presence of muscle weakness at birth (congenital), and abnormal muscle biopsies. CMD results in generalized weakness, and usually progresses slowly. A subtype, called Fukuyama CMD, also involves mental retardation and is more common in Japan.

Genetic profile

The muscular dystrophies are genetic conditions, meaning they are caused by alterations in genes. Genes, which are linked together on **chromosomes**, have two functions; they code for the production of proteins, and they are the material of **inheritance**. Parents pass along genes to their children, providing them with a complete set of instructions for making their own proteins.

Because both parents contribute genetic material to their offspring, each child carries two copies of almost every **gene**, one from each parent. For some conditions to occur, both copies must be altered. Such conditions are called autosomal recessive conditions. Some forms of LGMD and DD exhibit this pattern of inheritance, as does CMD. A person with only one altered copy, called a carrier, will not have the condition, but may pass the altered gene on to his children. When two carriers have children, the chances of having a child with the condition is one in four for each pregnancy.

Other conditions occur when only one altered gene copy is present. Such conditions are called autosomal dominant conditions. DM, FSH, and OPMD, exhibit this pattern of inheritance, as do some forms of DD and LGMD. When a person affected by the condition has a child with someone not affected, the chances of having an affected child is one in two.

Because of chromosomal differences between the sexes, some genes are not present in two copies. The chromosomes that determine whether a person is male or female are called the X and Y chromosomes. A person with two X chromosomes is female, while a person with one X and one Y is male. While the X chromosome carries many genes, the Y chromosome carries almost none. Therefore, a male has only one copy of each gene on the X chromosome, and if it is altered, he will have the condition that alteration causes. Such conditions are said to be X-linked. X-linked conditions include DMD, BMD, and EDMD. Women are not usually affected by X-linked conditions, since they will likely have one unaltered copy between the two chromosomes. Some female carriers of DMD have a mild form of the condition, probably because their one unaltered gene copy is shut down in some of their cells.

Women carriers of X-linked conditions have a one in two chance of passing the altered gene on to each child born. Daughters who inherit the altered gene will be carriers. A son born without the altered gene will be free of the condition and cannot pass it on to his children. A son born with the altered gene will have the condition. He will pass the altered gene on to each of his daughters, who will then be carriers, but to none of his sons (because they inherit his Y chromosome).

Not all genetic alterations are inherited. As many as one third of the cases of DMD are due to new mutations that arise during egg formation in the mother. New mutations are less common in other forms of muscular dystrophy.

Several of the muscular dystrophies, including DMD, BMD, CMD, and most forms of LGMD, are due to alterations in the genes for a complex of muscle proteins. This complex spans the muscle cell membrane (a thin sheath that surrounds each muscle cell) to unite a fibrous network on the interior of the cell with a fibrous network on the outside. Theory holds that by linking these two networks, the complex acts as a "shock absorber," redistributing and evening out the forces generated by contraction of the muscle, thereby preventing rupture of the muscle membrane. Alterations in the proteins of the complex lead to deterioration of the muscle during normal contraction and relaxation cycles. Symptoms of these conditions set in as the muscle gradually exhausts its ability to repair itself.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Becker muscular dystrophy (BMD)—A type of muscular dystrophy that affects older boys and men, and usually follows a milder course than Duchenne muscular dystrophy.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Distal muscular dystrophy (DD)—A form of muscular dystrophy that usually begins in middle age or later, causing weakness in the muscles of the feet and hands.

Duchenne muscular dystrophy (DMD)—The most severe form of muscular dystrophy, DMD usually affects young boys and causes progressive muscle weakness, usually beginning in the legs.

Dystrophin—A protein that helps muscle tissue repair itself. Both Duchenne muscular dystrophy and Becker muscular dystrophy are caused by flaws in the gene that instructs the body how to make this protein.

Facioscapulohumeral muscular dystrophy (FSH)—This form of muscular dystrophy, also known as Landouzy-Dejerine condition, begins in late childhood to early adulthood and affects both men and women, causing weakness in the muscles of the face, shoulders, and upper arms.

Limb-girdle muscular dystrophy (LGMD)—Form of muscular dystrophy that begins in late childhood to early adulthood and affects both men and women, causing weakness in the muscles around the hips and shoulders.

Myotonic dystrophy—A form of muscular dystrophy, also known as Steinert's condition, characterized by delay in the ability to relax muscles after forceful contraction, wasting of muscles, as well as other abnormalities.

Oculopharyngeal muscular dystrophy (OPMD)—Form of muscular dystrophy affecting adults of both sexes, and causing weakness in the eye muscles and throat.

Both DMD and BMD are caused by alterations in the gene for the protein called dystrophin. The alteration leading to DMD prevents the formation of any dystrophin, while that of BMD allows some protein to be made, accounting for the differences in severity and age of onset between the two conditions. Differences among the other muscular dystrophies in terms of the muscles involved and the ages of onset are less easily explained.

A number of genes have been found to cause LGMD. A majority of the more severe autosomal recessive types of LGMD with childhood-onset are caused by alterations in the genes responsible for making proteins called sarcoglycans. The sarcoglycans are a complex of proteins that are normally located in the muscle cell membrane along with dystrophin. Loss of these proteins causes the muscle cell membrane to lose some of its shock absorber qualities. The genes responsible include LGMD2D on chromosome 17, which codes for the alpha-sarcoglycan protein; LGMD2E on chromosome 4, which codes for the beta-sarcoglycan protein; LGMD2C on chromosome 13, which codes for the gamma-sarcoglycan protein; and LGMD2F on chromosome 5, which codes for the delta-sarcoglycan protein. Some cases of autosomal recessive LGMD are caused by an alteration in a gene, LGMD2A, on chromosome 15, which codes for a muscle enzyme, calpain 3. The relationship between this alteration and the symptoms of the condition is unclear. Alterations in a gene called LGMD2B on chromosome 2 that codes for the dysferlin protein, is also responsible for a minority of autosomal recessive LGMD

cases. The exact role of dysferlin is not known. Finally, alterations in the LGMD2G gene on chromosome 17 which codes for a protein, telethonin, is responsible for autosomal recessive LGMD in two reported families. The exact role of telethonin is not known. Some families with autosomal recessive LGMD are not accounted for by alterations in any of the above mentioned genes, indicating that there are as yet undiscovered genes that can cause LGMD. The autosomal dominant LGMD genes have mostly been described in single families. These types of LGMD are considered quite rare.

The genes causing these types of LGMD, their chromosomal location, and the proteins they code for (when known) are listed below:

- LGMD1A (chromosome 5): myotilin
- LGMD1B (chromosome 1): laminin
- LGMD1C (chromosome 3): caveolin
- LGMD1D (chromosome 6)
- LGMD1E (chromosome 7)
- COL6A1 (chromosome 21): collagen VI alpha 1
- COL6A2 (chromosome 21): collagen VI alpha 2
- COL6A3 (chromosome 2): collagen VI alpha 3

The causes of the other muscular dystrophies are not as well understood:

- EDMD is due to a alteration in the gene for a protein called emerin, which is found in the membrane of a cell's nucleus, but whose exact function is unknown.
- Myotonic dystrophy is caused by alterations in a gene on chromosome 19 for an enzyme called myotonin protein kinase that may control the flow of charged particles within muscle cells. This gene alteration is called a triple repeat, meaning it contains extra triplets of **DNA** code. It is possible that this alteration affects nearby genes as well, and that the widespread symptoms of myotonic dystrophy are due to a range of genetic disruptions.
- The gene for OPMD appears to also be altered with a triple repeat. The function of the affected protein may involve translation of genetic messages in a cell's nucleus.
- The gene(s) for FSH is located on the long arm of chromosome 4 at gene location 4q35. Nearly all cases of FSH are associated with a deletion (missing piece) of genetic material in this region. Researchers are investigating the molecular connection of this deletion and FSH. It is not yet certain whether the deleted material contains an active gene or changes the regulation or activity of a nearby FSH gene. A small number of FSH cases are not linked to chromosome 4. Their linkage to any other chromosome or genetic feature is under investigation.
- The gene(s) responsible for DD have not yet been found.
- About 50% of individuals with CMD have their condition as a result of deficiency in a protein called merosin, which is made by a gene called laminin. The merosin protein usually lies outside muscle cells and links them to the surrounding tissue. When merosin is not produced, the muscle fibers degenerate soon after birth. A second gene called integrin is responsible for CMD in a few individuals but alterations in this gene are a rare cause of CMD. The gene responsible for Fukuyama CMD is FCMD and it is responsible for making a protein called fukutin whose function is not clear.

Signs and symptoms

All of the muscular dystrophies are marked by muscle weakness as the major symptom. The distribution of symptoms, age of onset, and progression differ significantly. Pain is sometimes a symptom of each, usually due to the effects of weakness on joint position.

DUCHENNE MUSCULAR DYSTROPHY (DMD) A boy with Duchenne muscular dystrophy usually begins to show symptoms as a pre-schooler. The legs are affected first, making walking difficult and causing balance problems. Most patients walk three to six months later than expected and have difficulty running. Later on, a boy with DMD will push his hands against his knees to rise to a standing position, to compensate for leg weakness. About the same time, his calves will begin to enlarge, though with fibrous tissue rather than with muscle, and feel firm and rubbery; this condition gives DMD one of its alternate names, pseudohypertrophic muscular dystrophy. He will widen his stance to maintain balance, and walk with a waddling gait to advance his weakened legs. Contractures (permanent muscle tightening) usually begin by age five or six, most severely in the calf muscles. This pulls the foot down and back, forcing the boy to walk on tip-toes, and further decreases balance. Climbing stairs and rising unaided may become impossible by age nine or ten, and most boys use a wheelchair for mobility by the age of 12. Weakening of the trunk muscles around this age often leads to **scoliosis** (a side-to-side spine curvature) and kyphosis (a front-to-back curvature).

The most serious weakness of DMD is weakness of the diaphragm, the sheet of muscles at the top of the abdomen that perform the main work of breathing and coughing. Diaphragm weakness leads to reduced energy

and stamina, and increased lung infection because of the inability to cough effectively. Young men with DMD often live into their twenties and beyond, provided they have mechanical ventilation assistance and good respiratory hygiene.

Among males with DMD, the incidence of cardiomyopathy (weakness of the heart muscle), increases steadily in teenage years. Almost all patients have cardiomyopathy after 18 years of age. It has also been shown that carrier females are at increased risk for cardiomyopathy and should also be screened.

About one third of males with DMD experience specific learning disabilities, including difficulty learning by ear rather than by sight and difficulty paying attention to long lists of instructions. Individualized educational programs usually compensate well for these disabilities.

BECKER MUSCULAR DYSTROPHY (BMD) The symptoms of BMD usually appear in late childhood to early adulthood. Though the progression of symptoms may parallel that of DMD, the symptoms are usually milder and the course more variable. The same pattern of leg weakness, unsteadiness, and contractures occur later for the young man with BMD, often allowing independent walking into the twenties or early thirties. Scoliosis may occur, but is usually milder and progresses more slowly. Cardiomyopathy occurs more commonly in BMD. Problems may include irregular heartbeats (arrhythmias) and congestive heart failure. Symptoms may include fatigue, shortness of breath, chest pain, and dizziness. Respiratory weakness also occurs, and may lead to the need for mechanical ventilation.

EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD) This type of muscular dystrophy usually begins in early childhood, often with contractures preceding muscle weakness. Weakness affects the shoulder and upper arm initially, along with the calf muscles, leading to foot-drop. Most men with EDMD survive into middle age, although an abnormality in the heart's rhythm (heart block) may be fatal if not treated with a pacemaker.

LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMD) While there are several genes that cause the various types of LGMD, two major clinical forms of LGMD are usually recognized. A severe childhood form is similar in appearance to DMD, but is inherited as an autosomal recessive trait. Symptoms of adult-onset LGMD usually appear in a person's teens or twenties, and are marked by progressive weakness and wasting of the muscles closest to the trunk. Contractures may occur, and the ability to walk is usually lost about 20 years after onset. Some people with LGMD develop respiratory weakness that requires use of a ventilator. Life-span may be somewhat shortened. Autosomal dominant forms usually occur later in life and progress relatively slowly.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSH) FSH varies in its severity and age of onset, even among members of the same family. Symptoms most commonly begin in the teens or early twenties, though infant or childhood onset is possible. Symptoms tend to be more severe in those with earlier onset. The condition is named for the regions of the body most severely affected by the condition: muscles of the face (facio-), shoulders (scapulo-), and upper arms (humeral). Hips and legs may be affected as well. Children with FSH may develop partial or complete deafness.

The first symptom noticed is often difficulty lifting objects above the shoulders. The weakness may be greater on one side than the other. Shoulder weakness also causes the shoulder blades to jut backward, called scapular winging. Muscles in the upper arm often lose bulk sooner than those of the forearm, giving a "Popeye" appearance to the arms. Facial weakness may lead to loss of facial expression, difficulty closing the eyes completely, and inability to drink through a straw, blow up a balloon, or whistle. A person with FSH may not be able to wrinkle thier forehead. Contracture of the calf muscles may cause foot-drop, leading to frequent tripping over curbs or rough spots. People with earlier onset often require a wheelchair for mobility, while those with later onset rarely do.

MYOTONIC DYSTROPHY Symptoms of myotonic dystrophy include facial weakness and a slack jaw, drooping eyelids (ptosis), and muscle wasting in the forearms and calves. A person with myotonic dystrophy has difficulty relaxing his grasp, especially if the object is cold. Myotonic dystrophy affects heart muscle, causing arrhythmias and heart block, and the muscles of the digestive system, leading to motility disorders and constipation. Other body systems are affected as well; myotonic dystrophy may cause cataracts, retinal degeneration, mental deficiency, frontal balding, skin disorders, testicular atrophy, sleep apnea, and insulin resistance. An increased need or desire for sleep is common, as is diminished motivation. The condition is extremely variable; some individuals show profound weakness as a newborn (congenital myotonic dystrophy), others show mental retardation in childhood, many show characteristic facial features and muscle wasting in adulthood, while the most mildly affected individuals show only cataracts in middle age with no other symptoms. Individuals with a severe form of mytonic dystropy typically have severe disabilites within 20 years of onset, although most do not require a wheelchair even late in life.

OCULOPHARYNGEAL MUSCULAR DYSTROPHY (OPMD) OPMD usually begins in a person's thirties or

forties, with weakness in the muscles controlling the eyes and throat. Symptoms include drooping eyelids, and difficulty swallowing (dysphagia). Weakness progresses to other muscles of the face, neck, and occasionally the upper limbs. Swallowing difficulty may cause aspiration, or the introduction of food or saliva into the airways. Pneumonia may follow.

DISTAL MUSCULAR DYSTROPHY (DD) DD usually begins in the twenties or thirties, with weakness in the hands, forearms, and lower legs. Difficulty with fine movements such as typing or fastening buttons may be the first symptoms. Symptoms progress slowly, and the condition usually does not affect life span.

CONGENITAL MUSCULAR DYSTROPHY (CMD) CMD is marked by severe muscle weakness from birth, with infants displaying "floppiness," very poor muscle tone, and they often have trouble moving their limbs or head against gravity. Mental function is normal but some are never able to walk. They may live into young adulthood or beyond. In contrast, children with Fukuyama CMD are rarely able to walk, and have severe mental retardation. Most children with this type of CMD die in childhood.

Diagnosis

The diagnosis of muscular dystrophy involves a careful medical history and a thorough physical exam to determine the distribution of symptoms and to rule out other causes. Family history may give important clues, since all the muscular dystrophies are genetic conditions (though no family history will be evident in the event of new mutations; in autosomal recessive inheritance, the family history may also be negative).

Lab tests may include:

- Blood level of the muscle enzyme creatine kinase (CK). CK levels rise in the blood due to muscle damage, and may be seen in some conditions even before symptoms appear.
- Muscle biopsy, in which a small piece of muscle tissue is removed for microscopic examination. Changes in the structure of muscle cells and presence of fibrous tissue or other aberrant structures are characteristic of different forms of muscular dystrophy. The muscle tissue can also be stained to detect the presence or absence of particular proteins, including dystrophin.
- Electromyogram (EMG). This electrical test is used to examine the response of the muscles to stimulation. Decreased response is seen in muscular dystrophy. Other characteristic changes are seen in DM.
- Genetic tests. Several of the muscular dystrophies can be positively identified by testing for the presence of the altered gene involved. Accurate genetic tests are available for DMD, BMD, DM, several forms of LGMD, and EDMD. **Genetic testing** for some of these conditions in future pregnancies of an affected individual or parents of an affected individual can be done before birth through **amniocentesis** or chorionic villus sampling. Prenatal testing can only be undertaken after the diagnosis in the affected individual has been genetically confirmed and the couple has been counseled regarding the risks of recurrence.
- Other specific tests as necessary. For EDMD, DMD and BMD, for example, an electrocardiogram may be needed to test heart function, and hearing tests are performed for children with FSH.

For most forms of muscular dystrophy, accurate diagnosis is not difficult when done by someone familiar with the range of conditions. There are exceptions, however. Even with a muscle biopsy, it may be difficult to distinguish between FSH and another muscle condition, polymyositis. Childhood-onset LGMD is often mistaken for the much more common DMD, especially when it occurs in boys. BMD with an early onset appears very similar to DMD, and a genetic test may be needed to accurately distinguish them. The muscular dystrophies may be confused with conditions involving the motor neurons, such as **spinal muscular atrophy**; conditions of the neuromuscular junction, such as **myasthenia gravis**; and other muscle conditions, as all involve generalized weakness of varying distribution.

Prenatal diagnosis (testing of the baby while in the womb) can be done for those types of muscular dystrophy where the specific disease-causing gene alteration has been identified in a previously affected family member. Prenatal diagnosis can be done utilizing DNA extracted from tissue obtained by chorionic villus sampling or amniocentesis.

Treatment and management

Drugs

There are no cures for any of the muscular dystrophies. Prednisone, a corticosteroid, has been shown to delay the progression of DMD somewhat, for reasons that are still unclear. Some have reported improvement in strength and function in patients treated with a single dose. Improvement begins within ten days and plateaus after three months. Long-term benefit has not been demonstrated. Prednisone is also prescribed for BMD, though no controlled studies have tested its benefit. A study is under way in the use of gentamicin, an antibiotic that may slow down the symptoms of DMD in a small number of cases. No other drugs are currently known to have an effect on the course of any other muscular dystrophy.

Treatment of muscular dystrophy is mainly directed at preventing the complications of weakness, including decreased mobility and dexterity, contractures, scoliosis, heart alterations, and respiratory insufficiency.

Physical therapy

Physical therapy, regular stretching in particular, is used to maintain the range of motion of affected muscles and to prevent or delay contractures. Braces are used as well, especially on the ankles and feet to prevent tip-toeing. Full-leg braces may be used in children with DMD to prolong the period of independent walking. Strengthening other muscle groups to compensate for weakness may be possible if the affected muscles are few and isolated, as in the earlier stages of the milder muscular dystrophies. Regular, nonstrenuous exercise helps maintain general good health. Strenuous exercise is usually not recommended, since it may damage muscles further.

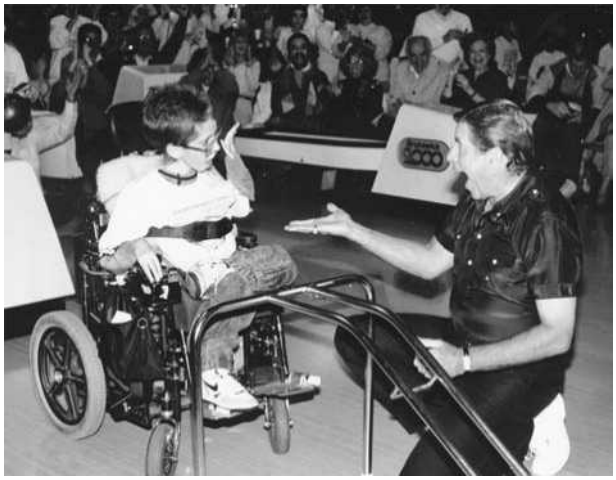
Surgery

When contractures become more pronounced, tenotomy surgery may be performed. In this operation, the tendon of the contractured muscle is cut, and the limb is braced in its normal resting position while the tendon regrows. In FSH, surgical fixation of the scapula can help compensate for shoulder weakness. For a person with OPMD, surgical lifting of the eyelids may help compensate for weakened muscular control. For a person with DM, sleep apnea may be treated surgically to maintain an open airway. Scoliosis surgery is often needed in boys with DMD, but much less often in other muscular dystrophies. Surgery is recommended at a much lower degree of curvature for DMD than for scoliosis due to other conditions, since the decline in respiratory function in DMD makes surgery at a later time dangerous. In this surgery, the vertebrae are fused together to maintain the spine in the upright position. Steel rods are inserted at the time of operation to keep the spine rigid while the bones grow together.

When any type of surgery is performed in patients with muscular dystrophy, anesthesia must be carefully selected. People with MD are susceptible to a severe reaction, known as **malignant hyperthermia**, when given halothane anesthetic.

Occupational therapy

The occupational therapist suggests techniques and tools to compensate for the loss of strength and dexterity. Strategies may include modifications in the home, adaptive utensils and dressing aids, compensatory movements and positioning, wheelchair accessories, or communication aids.



The *Jerry Lewis MDA Labor Day Telethon* raises millions of dollars for muscular dystrophy research and programs each year. *(Muscular Dystrophy Association)*

Nutrition

Good nutrition helps to promote general health in all the muscular dystrophies. No special diet or supplement has been shown to be of use in any of the conditions. The weakness in the throat muscles seen especially in OPMD and later DMD may necessitate the use of a gastrostomy tube, inserted in the stomach to provide nutrition directly.

Cardiac care

The arrhythmias of EDMD and BMD may be treatable with antiarrhythmia drugs. A pacemaker may be implanted if these do not provide adequate control. Heart transplants are increasingly common for men with BMD. A complete cardiac evaluation is recommended at least once in all carrier females of DMD and EDMD.

Respiratory care

People who develop weakness of the diaphragm or other ventilatory muscles may require a mechanical ventilator to continue breathing deeply enough. Air may be administered through a nasal mask or mouthpiece, or through a tracheostomy tube, which is inserted through a surgical incision through the neck and into the windpipe. Most people with muscular dystrophy do not need a tracheostomy, although some may prefer it to continual use of a mask or mouthpiece. Supplemental oxygen is not needed. Good hygiene of the lungs is critical for health and long-term survival of a person with weakened ventilatory muscles. Assisted cough techniques provide the strength needed to clear the airways of secretions; an assisted cough machine is also available and provides excellent results.

Experimental treatments

Two experimental procedures aiming to cure DMD have attracted a great deal of attention in the past decade. In myoblast transfer, millions of immature muscle cells are injected into an affected muscle. The goal of the treatment is to promote the growth of the injected cells, replacing the abnormal host cells with healthy new ones. Myoblast transfer is under investigation but remains experimental.

Gene therapy introduces unaltered copies of the altered gene into muscle cells. The goal is to allow the existing muscle cells to use the new gene to produce the protein it cannot make with its abnormal gene. Problems with gene therapy research have included immune rejection of the virus used to introduce the gene, loss of gene function after several weeks, and an inability to get the gene to enough cells to make a functional difference in the affected muscle. Researchers are preparing for the first gene therapy trial for LGMD in the United States. The goal will be to replace the missing sarcoglycan gene(s).

Genetic counseling

Individuals with muscular dystrophy and their families may benefit from **genetic counseling** for information on the condition and recurrence risks for future pregnancies.

Prognosis

The expected lifespan for a male with DMD has increased significantly in the past two decades. Most young men will live into their early or mid-twenties. Respiratory infections become an increasing problem as their breathing becomes weaker, and these infections are usually the cause of death.

The course of the other muscular dystrophies is more variable; expected life spans and degrees of disability are hard to predict, but may be related to age of onset and initial symptoms. Prediction is made more difficult because, as new genes are discovered, it is becoming clear that several of the dystrophies are not uniform disorders, but rather symptom groups caused by different genes.

People with dystrophies with significant heart involvement (BMD, EDMD, myotonic dystrophy) may nonetheless have almost normal life spans, provided that cardiac complications are monitored and treated aggressively. The respiratory involvement of BMD and LGMD similarly require careful and prompt treatment.

Prevention

There is no way to prevent any of the muscular dystrophies in a person who has the genes responsible for these disorders. Accurate genetic tests, including prenatal tests, are available for some of the muscular dystrophies. Results of these tests may be useful for purposes of family planning.

Resources

BOOKS

Emery, Alan. *Muscular Dystrophy: The Facts.* Oxford Medical Publications, 1994.

Swash, Michael, and Martin Schwartz. *Neuromuscular Conditions: A Practical Approach to Diagnosis and Management*, 3rd edition. Springer, 1997.

ORGANIZATIONS

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

Online Myotonic & Congenital Dystrophies Support Group International. 185 Unionville Road, Freedom, PA 15042. (724)775-9448 or (724)774-0261. <http://www.angelfire.com/pa2/MyotonicDystrophy/index.html>.

Nada Quercia, Msc, CCGC

Myasthenia gravis

Definition

Myasthenia gravis is an autoimmune disease that causes muscle weakness.

Description

The name myasthenia gravis literally means “grave muscle weakness”. Myasthenia gravis (MG) affects the neuromuscular junction, interrupting the communication between nerve and muscle, and thereby causing weakness. A person with MG may have difficulty moving their eyes, walking, speaking clearly, swallowing, and even breathing, depending on the severity and distribution of weakness. Increased weakness with exertion, and improvement with rest, is a characteristic feature of MG.

Genetic profile

Myasthenia gravis is not inherited directly nor is it contagious. It is usually considered sporadic, meaning that it occurs by chance. One to four percent of cases are familial, which means they occur more than once in a family. Predisposition in a family to develop myasthenia gravis may be due to autoimmunity in general.

Demographics

About 36,000 people in the United States are affected by MG; roughly 14 people per 100,000. It can occur at any age, but is most common in women under age 40, and in men who are over 60. Occasionally the disease is present in more than one person in a family.

Signs and symptoms

Myasthenia gravis is an autoimmune disease, meaning it is caused by the body's own immune system. In MG, the immune system attacks a receptor on the surface of muscle cells. This prevents the muscle from receiving the nerve impulses that normally make it respond. MG affects "voluntary" muscles, which are those muscles under conscious control responsible for movement. It does not affect heart muscle or the "smooth" muscle found in the digestive system and other internal organs.

A muscle is stimulated to contract when the nerve cell controlling it releases acetylcholine molecules onto its surface. The acetylcholine lands on a muscle protein called the acetylcholine receptor. This leads to rapid chemical changes in the muscle, which cause it to contract. Acetylcholine is then broken down by acetylcholinesterase enzyme, to prevent further stimulation.

In MG, immune cells create antibodies against the acetylcholine receptor. Antibodies are proteins normally involved in fighting infection. When these antibodies attach to the receptor, they prevent it from receiving acetylcholine, decreasing the ability of the muscle to respond to stimulation.

Why the immune system creates these self-reactive "autoantibodies" is unknown, although there are several hypotheses:

- During fetal development, the immune system generates many B cells that can make autoantibodies, but B cells that could harm the body's own tissues are screened out and destroyed before birth. It is possible that the stage is set for MG when some of these cells escape detection.
- Genes controlling other parts of the immune system, called MHC genes, appear to influence how susceptible a person is to developing autoimmune disease.
- Infection may trigger some cases of MG. When activated, the immune system may mistake portions of the acetylcholine receptor for portions of an invading virus, though no candidate virus has yet been identified conclusively.
- About 10% of those with MG also have thymomas, or benign tumors of the thymus gland. The thymus is a principal organ of the immune system, and researchers speculate that thymic irregularities are involved in the progression of MG.

Some or all of these factors (developmental, genetic, infectious, and thymic) may interact to create the autoimmune reaction.

The earliest symptoms of MG often result from weakness of the extraocular muscles, which control eye movements. Symptoms involving the eye (ocular symptoms) include double vision (diplopia), especially when not gazing straight ahead, and difficulty raising the eyelids (ptosis). A person with ptosis may need to tilt their head back to see. Eye-related symptoms remain the only symptoms for about 15% of MG patients. Another common early symptom is difficulty chewing and swallowing, due to weakness in the bulbar muscles, which are in the mouth and throat. Choking becomes more likely, especially with food that requires extensive chewing.

Weakness usually becomes more widespread within several months of the first symptoms, reaching their maximum within a year in two-thirds of patients. Weakness may involve muscles of the arms, legs, neck, trunk, and face, and affect the ability to lift objects, walk, hold the head up, and speak.

KEY TERMS

Antibody—A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

Autoantibody—An antibody that reacts against part of the self.

Autoimmune disease—Describes a group of diseases characterized by an inflammatory immune reaction erroneously directed toward 'self' tissues.

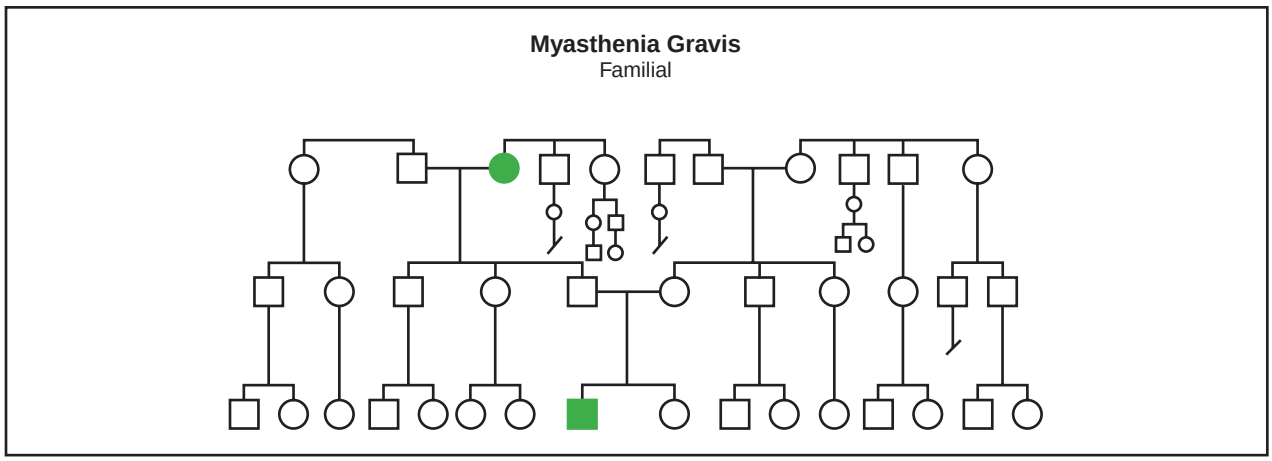
Bulbar muscles—Muscles that control chewing, swallowing, and speaking.

Neuromuscular junction—The site at which nerve impulses are transmitted to muscles.

Pyridostigmine bromide (Mestinon)—An anticholinesterase drug used in treating myasthenia gravis.

Tensilon test—A test for diagnosing myasthenia gravis. Tensilon is injected into a vein and, if the person has MG, their muscle strength will improve for about five minutes.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.



Familial inheritance of Myasthenia gravis. *(Gale Group)*

Symptoms of MG become worse upon exertion and better with rest. Heat, including heat from the sun, hot showers, and hot drinks, may increase weakness. Infection and stress may worsen symptoms. Symptoms may vary from day to day and month to month, with intervals of no weakness interspersed with a progressive decline in strength.

Myasthenic crisis may occur, in which the breathing muscles become too weak to provide adequate respiration. Symptoms include weak and shallow breathing, shortness of breath, pale or bluish skin color, and a racing heart. Myasthenic crisis is an emergency condition requiring immediate treatment. In patients treated with anticholinesterase agents, myasthenic crisis must be differentiated from cholinergic crisis related to overmedication.

Pregnancy worsens MG in about one third of women, has no effect in one third, and improves symptoms in another third. About 12% of infants born to women with MG have neonatal myasthenia, a temporary but potentially life-threatening condition. It is caused by the transfer of maternal antibodies into the fetal circulation just before birth. Symptoms include weakness, poor muscle tone, feeble cry, and difficulty feeding. The infant may have difficulty breathing, requiring the use of a ventilator. Neonatal myasthenia usually clears up within a month.

Diagnosis

Myasthenia gravis is often diagnosed accurately by a careful medical history and a neuromuscular exam, but several tests are used to confirm the diagnosis. Other conditions causing worsening of bulbar and skeletal muscles must be considered, including drug-induced myasthenia, thyroid disease, Lambert-Eaton myasthenic syndrome, botulism, and inherited muscular dystrophies.

MG causes characteristic changes in the electrical responses of muscles that may be observed with an electromyogram, which measures muscular response to electrical stimulation. Repetitive nerve stimulation leads to reduction in the height of the measured muscle response, reflecting the muscle's tendency to become fatigued.

Blood tests may confirm the presence of the antibody to the acetylcholine receptor, though up to a quarter of MG patients will not have detectable levels. A chest x ray or chest computed tomography scan (CT scan) may be performed to look for thymoma.

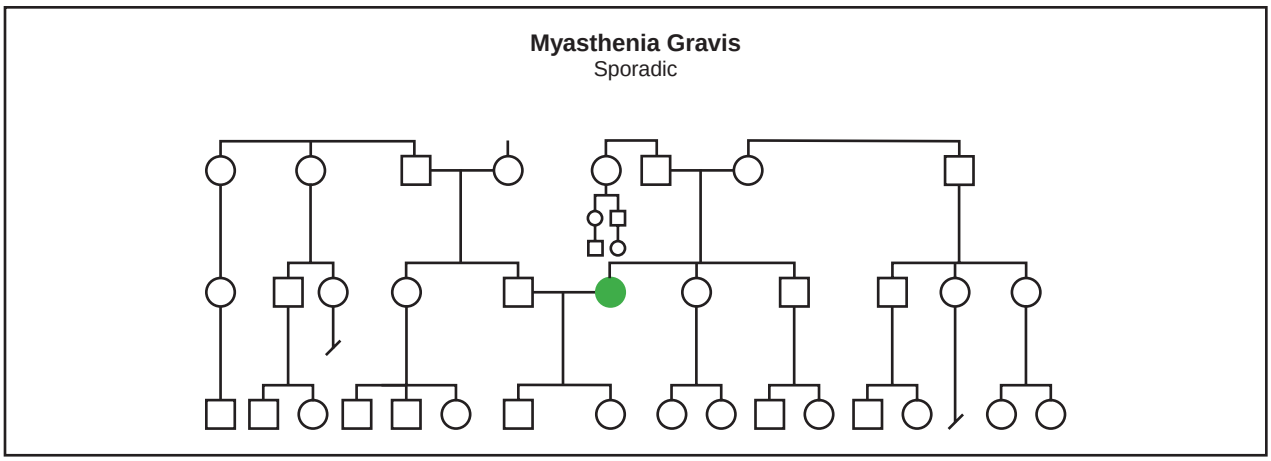
Treatment and management

While there is no cure for myasthenia gravis, there are a number of treatments that effectively control symptoms in most people.

Edrophonium (Tensilon) blocks the action of acetylcholinesterase, prolonging the effect of acetylcholine and increasing strength. An injection of edrophonium rapidly leads to a marked improvement in most people with MG. An alternate drug, neostigmine, may also be used.

Pyridostigmine (Mestinon) is usually the first drug prescribed. Like edrophonium, pyridostigmine blocks acetylcholinesterase. It is longer-acting, taken by mouth, and well-tolerated. Loss of responsiveness and disease progression combine to eventually make pyridostigmine ineffective in tolerable doses in many patients.

Thymectomy, or removal of the thymus gland, has increasingly become standard treatment for MG. Up to 85% of people with MG improve after thymectomy, with complete remission eventually seen in about 30%. The



Sporatic occurance of Myathenia gravis in a family. *(Gale Group)*

improvement may take months or even several years to fully develop. Thymectomy is not usually recommended for children with MG, since the thymus continues to play an important immune role throughout childhood.

Immune-suppressing drugs are used to treat MG if response to pyridostigmine and thymectomy are not adequate. Drugs include corticosteroids such as prednisone, and the non-steroids azathioprine (Imuran) and cyclosporine (Sandimmune).

Plasma exchange may be performed to treat myasthenic crisis or to improve very weak patients before thymectomy. In this procedure, blood plasma is removed and replaced with purified plasma free of autoantibodies. It can produce a temporary improvement in symptoms, but is too expensive for long-term treatment. Another blood treatment, intravenous immunoglobulin therapy, is also used for myasthenic crisis. In this procedure, large quantities of purified immune proteins (immunoglobulins) are injected. For unknown reasons, this leads to symptomatic improvement in up to 85% of patients. It is also too expensive for long-term treatment.

People with weakness of the bulbar muscles may need t3o eat softer foods that are easier to chew and swallow. In more severe cases, it may be necessary to obtain nutrition through a feeding tube placed into the stomach (gastrostomy tube).

Some drugs should be avoided by people with MG because they interfere with normal neuromuscular function. Drugs to be avoided or used with caution include:

- Many types of antibiotics, including erythromycin, streptomycin, and ampicillin
- Some cardiovascular drugs, including Verapamil, betaxolol, and propranolol
- Some drugs used in psychiatric conditions, including chlorpromazine, clozapine, and lithium.

Many other drugs may worsen symptoms as well, so patients should check with the doctor who treats their MG before taking any new medications.

A Medic-Alert card or bracelet provides an important source of information to emergency providers about the special situation of a person with MG. They are available from health care providers.

Prognosis

Most people with MG can be treated successfully enough to prevent their condition from becoming debilitating. In some cases, however, symptoms may worsen even with vigorous treatment, leading to generalized weakness and disability. MG rarely causes early death except from myasthenic crisis. There is no known way to prevent myasthenia gravis. Thymectomy improves symptoms significantly in many patients, and relieves them entirely in some. Avoiding heat can help minimize symptoms.

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ORGANIZATIONS

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

Myasthenia Gravis Foundation of America. 5841 Cedar Lake Rd., Suite 204, Minneapolis, MN 55416. (800) 541-5454. Fax: (952) 545-6073.

WEBSITES

Immune Deficiency Foundation. <http://www.primaryimmune.org>.

Myasthenia Gravis Foundation of America <http://www.myasthenia.org>.

National Institute of Neurological Disorders and Stroke Fact Sheet on Myasthenia Gravis. <http://www.ninds.nih.gov/health_and_medical/pubs/myasthenia_gravis.htm>.

Catherine L. Tesla, MS, CGC

Myopia

Definition

Myopia is the medical term for nearsightedness. People with myopia see objects more clearly when they are close to the eye, while distant objects appear blurred or fuzzy. Reading and close-up work may be clear, but distance vision is blurry.

Description

To understand myopia it is necessary to have a basic knowledge of the main parts of the eye's focusing system: the cornea, the lens, and the retina. The cornea is a tough, transparent, dome-shaped tissue that covers the front of the eye (not to be confused with the white, opaque sclera). The cornea lies in front of the iris (the colored part of the eye). The lens is a transparent, double-convex structure located behind the iris. The retina is a thin membrane that lines the rear of the eyeball. Light-sensitive retinal cells convert incoming light rays into electrical signals that are sent along the optic nerve to the brain, which then interprets the images.

In people with normal vision, parallel light rays enter the eye and are bent by the cornea and lens (a process called refraction) to focus precisely on the retina, providing a crisp, clear image. In the myopic eye, the focusing power of the cornea (the major refracting structure of the eye) and the lens is too great with respect to the length of the eyeball. Light rays are bent too much, and they converge in front of the retina. This inaccuracy is called a refractive error. In other words, an overfocused fuzzy image is sent to the brain.

There are many types of myopia. Some common types include:

- Physiologic
- Pathologic
- Acquired.

By far the most common form, physiologic myopia develops in children sometime between the ages of five and 10 years and gradually progresses until the eye is fully grown. Physiologic myopia may include refractive myopia (the cornea and lens-bending properties are too strong) and axial myopia (the eyeball is too long). Pathologic myopia is a far less common abnormality. This condition begins as physiologic myopia, but rather than stabilizing, the eye continues to enlarge at an abnormal rate (progressive myopia). This more advanced type of myopia may lead to degenerative changes in the eye (degenerative myopia). Acquired myopia occurs after infancy. This condition may be seen in association with uncontrolled diabetes and certain types of cataracts. Antihypertensive drugs and other medications can also affect the refractive power of the lens.

Genetic profile

Eye care professionals have debated the role of genetics in the development of myopia for many years. Some believe that a tendency toward myopia may be inherited, but the actual disorder results from a combination of environmental and genetic factors. Environmental factors include close work; work with computer monitors or other instruments that emit some light (electron microscopes, photographic equipment, lasers, etc.); emotional stress; and eye strain.

A variety of genetic patterns for inheriting myopia have been suggested, ranging from a recessive pattern with complete penetrance in people who are homozygotic for myopia to an autosomal dominant pattern; an autosomal recessive pattern; and various mixtures of these patterns. One explanation for this lack of agreement is that the genetic profile of high myopia (defined as a refractive error greater than -6 diopters) may differ from that of low myopia. Some researchers think that high myopia is determined by genetic factors to a greater extent than low myopia.

Another explanation for disagreement regarding the role of heredity in myopia is the sensitivity of the human eye to very small changes in its anatomical structure. Since even small deviations from normal structure cause significant refractive errors, it may be difficult to single out any specific genetic or environmental factor as their cause.

KEY TERMS

Accommodation—The ability of the lens to change its focus from distant to near objects. It is achieved through the action of the ciliary muscles that change the shape of the lens.

Cornea—The transparent structure of the eye over the lens that is continous with the sclera in forming the outermost, protective, layer of the eye.

Diopter (D)—A unit of measure for describing refractive power.

Laser-assisted in-situ keratomileusis (LASIK)—A procedure that uses a cutting tool and a laser to modify the cornea and correct moderate to high levels of myopia.

Lens—The transparent, elastic, curved structure behind the iris (colored part of the eye) that helps focus light on the retina.

Ophthalmologist—A physician specializing in the medical and surgical treatment of eye disorders.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Optometrist—A medical professional who examines and tests the eyes for disease and treats visual disorders by prescribing corrective lenses and/or vision therapy. In many states, optometrists are licensed to use diagnostic and therapeutic drugs to treat certain ocular diseases.

Orthokeratology—A method of reshaping the cornea using a contact lens. It is not considered a permanent method to reduce myopia.

Peripheral vision—The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

Photorefractive keratectomy (PRK)—A procedure that uses an excimer laser to make modifications to the cornea and permanently correct myopia. As of early 1998, only two lasers have been approved by the FDA for this purpose.

Radial keratotomy (RK)—A surgical procedure involving the use of a diamond-tipped blade to make several spoke-like slits in the peripheral (non-viewing) portion of the cornea to improve the focus of the eye and correct myopia by flattening the cornea.

Refraction—The bending of light rays as they pass from one medium through another. Used to describe the action of the cornea and lens on light rays as they enter they eye. Also used to describe the determination and measurement of the eye's focusing system by an optometrist or ophthalmologist.

Refractive eye surgery—A general term for surgical procedures that can improve or correct refractive errors by permanently changing the shape of the cornea.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Visual acuity—The ability to distinguish details and shapes of objects.

Genetic markers and gene mapping

Since 1992, genetic markers that may be associated with genes for myopia have been located on human **chromosomes** 1, 2, 12, and 18. There is some genetic information on the short arm of chromosome 2 in highly myopic people. Genetic information for low myopia appears to be located on the short arm of chromosome 1, but it is not known whether this information governs the structure of the eye itself or vulnerability to environmental factors.

In 1998, a team of American researchers presented evidence that a **gene** for familial high myopia with an autosomal dominant transmission pattern could be mapped to human chromosome 18 in eight North American families. The same group also found a second locus for this form of myopia on human chromosome 12 in a large German/Italian family. In 1999, a group of French researchers found no linkage between chromosome 18 and 32 French families with familial high myopia. These findings have been taken to indicate that more than one gene is involved in the transmission of the disorder.

Family studies

It has been known for some years that a family history of myopia is one of the most important risk factors for developing the condition. Only 6-15% of children with myopia come from families in which neither parent is myopic. In families with one myopic parent, 23-40%

of the children develop myopia. If both parents are myopic, the rate rises to 33%-60% for their children. One American study found that children with two myopic parents are six times as likely to develop myopia themselves as children with only one or no myopic parents. The precise interplay of genetic and environmental factors in these family patterns, however, is not yet known.

One multigenerational study of Chinese patients indicated that third generation family members had a higher risk of developing myopia even if their parents were not myopic. The researchers concluded that, at least in China, the genetic factors in myopia have remained constant over the past three generations while the environmental factors have intensified. The increase in the percentage of people with myopia over the last 50 years in the United States has led American researchers to the same conclusion.

Demographics

Myopia is the most common eye disorder in humans around the world. It affects between 25% and 35% of the adult population in the United States and the developed countries, but is thought to affect as much as 40% of the population in some parts of Asia. Some researchers have found slightly higher rates of myopia in women than in men.

The age distribution of myopia in the United States varies considerably. Five-year-olds have the lowest rate of myopia (less than 5%) of any age group. The prevalence of myopia rises among children and adolescents in school until it reaches the 25%-35% mark in the young adult population. It declines slightly in the over-45 age group; about 20% of 65-year-olds have myopia. The figure drops to 14% for Americans over 70.

Other factors that affect the demographic distribution of myopia are income level and education. The prevalence of myopia is higher among people with above-average incomes and educational attainments. Myopia is also more prevalent among people whose work requires a great deal of close focusing, including work with computers.

Signs and symptoms

Myopia is said to be caused by an elongation of the eyeball. This means that the oblong (as opposed to normal spherical) shape of the myopic eye causes the cornea and lens to focus at a point in front of the retina. A more precise explanation is that there is an inadequate correlation between the focusing power of the cornea and lens and the length of the eye.

People are generally born with a small amount of hyperopia (farsightedness), but as the eye grows this decreases and myopia does not become evident until later. This change is one reason why some researchers think that myopia is an acquired rather than an inherited trait.

The symptoms of myopia are blurred distance vision, eye discomfort, squinting, and eye strain.

Diagnosis

The diagnosis of myopia is typically made during the first several years of elementary school when a teacher notices a child having difficulty seeing the chalkboard, reading, or concentrating. The teacher or school nurse often recommends an eye examination by an ophthalmologist or optometrist. An ophthalmologist—M.D. or D.O. (Doctor of Osteopathy)—is a medical doctor trained in the diagnosis and treatment of eye problems. Ophthalmologists also perform eye surgery. An optometrist (O.D.) diagnoses, manages, and/or treats eye and visual disorders. In many states, optometrists are licensed to use diagnostic and therapeutic drugs.

A patient's distance vision is tested by reading letters or numbers on a chart posted a set distance away (usually 20 ft). The doctor asks the patient to view images through a variety of lenses to obtain the best correction. The doctor also examines the inside of the eye and the retina. An instrument called a slit lamp is used to examine the cornea and lens. The eyeglass prescription is written in terms of diopters (D), which measure the degree of refractive error. Mild to moderate myopia usually falls between -1.00D and -6.00D. Normal vision is commonly referred to as 20/20 to describe the eye's focusing ability at a distance of 20 ft from an object. For example, 20/50 means that a myopic person must stand 20 ft away from an eye chart to see what a normal person can see at 50 ft. The larger the bottom number, the greater the myopia.

Treatment and management

People with myopia have three main options for treatment: eyeglasses, contact lenses, and for those who meet certain criteria, refractive eye surgery.

Eyeglasses

Eyeglasses are the most common method used to correct myopia. Concave glass or plastic lenses are placed in frames in front of the eyes. The lenses are ground to the thickness and curvature specified in the eyeglass prescription. The lenses cause the light rays to diverge so that they focus further back, directly on the retina, producing clear distance vision.

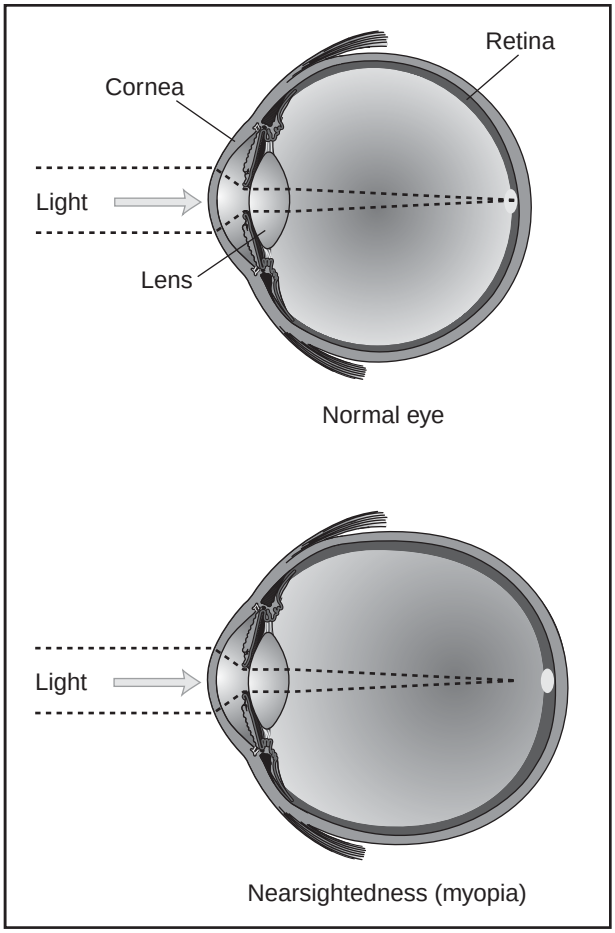
Contact lenses

Contact lenses are a second option for treatment. Contact lenses are extremely thin round discs of plastic that are worn on the eye in front of the cornea. Although there may be some initial discomfort, most people quickly grow accustomed to contact lenses. Hard contact lenses, made from a material called PMMA, are virtually obsolete. Rigid gas permeable lenses (RGP) are made of plastic that holds its shape but allows the passage of some oxygen into the eye. Some believe that RGP lenses may halt or slow the progression of myopia because they maintain a constant, gentle pressure that flattens the cornea. As of 2001, the National Eye Institute is conducting an ongoing study of RGP lenses called the Contact Lens and Myopia Progression (CLAMP) Study, with results to be published in 2003. A procedure called orthokeratology acts on this principle of "corneal molding;" however, when contact lenses are discontinued for a period of time, the cornea will generally go back to its original shape.

Soft contact lenses are made of flexible plastic and can be up to 80% water. Soft lenses offer increased comfort and the advantage of extended wear; some can be worn continuously for up to one week. While oxygen passes freely through soft lenses, bacterial contamination and other problems can occur, requiring replacement of lenses on a regular basis. It is very important to follow the cleaning and disinfecting regimens prescribed because protein and lipid buildup can occur on the lenses, causing discomfort or increasing the risk of infection. Contact lenses offer several benefits over glasses, including: better vision, less distortion, clear peripheral vision, and cosmetic appeal. In addition, contacts will not fog up from perspiration or changes in temperature.

Refractive eye surgery

For people who find glasses and contact lenses inconvenient or uncomfortable, and who meet selection criteria regarding age, degree of myopia, general health, etc., refractive eye surgery is a third treatment alternative. There are three types of corrective surgeries available as of 2001: 1) radial keratotomy (RK), 2) photorefractive keratectomy (PRK), and 3) laser-assisted in-situ keratomileusis (LASIK), which is still under clinical evaluation by the Food and Drug Administration (FDA). Refractive eye surgery improves myopic vision by permanently changing the shape of the cornea so that light rays focus properly on the retina. These procedures are performed on an outpatient basis and generally take 10-30 minutes.



This illustration compares the difference between a normal eye shape and light refraction versus a myopic eye. *(Gale Group)*

RADIAL KERATOTOMY Radial keratotomy (RK), the first of these procedures made available, has a high associated risk. It was first developed in Japan and the Soviet Union, and was introduced into the United States in 1978. The surgeon uses a delicate diamond-tipped blade, a microscope, and microscopic instruments to make several spoke-like "radial" incisions in the non-viewing (peripheral) portion of the cornea. As the incisions heal, the slits alter the curve of the cornea, making it more flat, which may improve the focus of images onto the retina.

PHOTOREFRACTIVE KERATECTOMY Photorefractive keratectomy (PRK) involves the use of a computer to measure the shape of the cornea. Using these measurements, the surgeon applies a computer-controlled laser to make modifications to the cornea. The PRK procedure flattens the cornea by vaporizing small amounts of tissue from the cornea's surface. As of early 2001, only two excimer lasers are approved by the FDA for PRK, although other lasers have been used. It is important to make sure

the laser being used is FDA approved. Photorefractive keratectomy can treat mild to moderate forms of myopia. The cost is approximately $2,000 per eye.

LASER-ASSISTED IN-SITU KERATOMILEUSIS Laser-assisted in-situ keratomileusis (LASIK) is the newest of these procedures. It is recommended for moderate to severe cases of myopia. A variation on the PRK method, LASIK uses lasers and a cutting tool called a microkeratome to cut a circular flap on the cornea. The flap is flipped back to expose the inner layers of the cornea. The cornea is treated with a laser to change the shape and focusing properties, then the flap is replaced.

Risks

All of these surgical procedures carry risks, the most serious being corneal scarring, corneal rupture, infection, cataracts, and loss of vision. In addition, a study published in March 2001 warns that mountain climbers who have had LASIK surgery should be aware of possible changes in their vision at high altitudes. The lack of oxygen at high altitudes causes temporary changes in the thickness of the cornea.

Since refractive eye surgery does not guarantee 20/20 vision, it is important to have realistic expectations before choosing this treatment. In a 10-year study conducted by the National Eye Institute between 1983 and 1993, over 50% of people with radial keratotomy gained 20/20 vision, and 85% passed a driving test (requiring 20/40 vision) after surgery, without glasses or contact lenses. Even if the patient gains near-perfect vision, however, there are potentially irritating side effects, such as postoperative pain, poor night vision, variation in visual acuity, light sensitivity and glare, and optical distortion. Refractive eye surgeries are considered elective procedures and are rarely covered by insurance plans.

Myopia treatments under research include corneal implants and permanent surgically placed contact lenses.

Alternative treatments

Some eye care professionals recommend treatments to help improve circulation, reduce eye strain, and relax the eye muscles. It is possible that by combining exercises with changes in behavior, the progression of myopia may be slowed or prevented. Alternative treatments include: visual therapy (also referred to as vision training or eye exercises); discontinuing close work; reducing eye strain (taking a rest break during periods of prolonged near vision tasks); and wearing bifocals to decrease the need to accommodate when doing close-up work.

Prognosis

Glasses and contact lenses can (but not always) correct the patient's vision to 20/20. Refractive surgery can make permanent improvements for the right candidates.

While the genetic factors that influence the transmission and severity of myopia cannot be changed, some environmental factors can be modified. They include reducing close work; reading and working in good light; taking frequent breaks when working at a computer or microscope for long periods of time; maintaining good nutrition; and practicing visual therapy (when recommended).

Eye strain can be prevented by using sufficient light for reading and close work, and by wearing corrective lenses as prescribed. Everyone should have regular eye examinations to see if their prescription has changed or if any other problems have developed. This is particularly important for people with high (degenerative) myopia who are at a greater risk of developing retinal detachment, retinal degeneration, **glaucoma**, or other problems.

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ORGANIZATIONS

American Academy of Ophthalmology. PO Box 7424, San Francisco, CA 94120-7424. (415) 561-8500. <http://www.eyenet.org>.

American Optometric Association. 243 North Lindbergh Blvd., St. Louis, MO 63141. (314) 991-4100. <http://www.aoanet.org>.

International Myopia Prevention Association. RD No. 5, Box 171, Ligonier, PA 15658. (412) 238-2101.

Myopia International Research Foundation. 1265 Broadway, Room 608, New York, NY 10001. (212) 684-2777.

National Eye Institute. Bldg. 31 Rm 6A32, 31 Center Dr., MSC 2510, Bethesda, MD 20892-2510. (301) 496-5248. 2020@nei.nih.gov. <http://www.nei.nih.gov>.

Rebecca J. Frey, PhD
Risa Palley Flynn

Myotonia atrophica *see* **Myotonic dystrophy**

Myotonic dystrophy

Definition

Myotonic dystrophy is a progressive disease in which the muscles are weak and are slow to relax after contraction.

Description

Myotonic dystrophy (DM), also called dystrophia myotonica, myotonia atrophica, or Steinert disease, is a common form of **muscular dystrophy**. DM is an inherited disease, affecting both males and females. About 30,000 people in the United States are affected. Symptoms may appear at any time from infancy to adulthood. DM causes general weakness, usually beginning in the muscles of the hands, feet, neck, or face. It slowly progresses to involve other muscle groups, including the heart. DM affects a wide variety of other organ systems as well.

A severe form of DM, congenital myotonic dystrophy, may appear in newborns of mothers who have DM. Congenital means that the condition is present from birth.

KEY TERMS

Electrocardiogram (ECG, EKG)—A test that uses electrodes attached to the chest with an adhesive gel to transmit the electrical impulses of the heart muscle to a recording device.

Electromyography (EMG)—A test that uses electrodes to record the electrical activity of muscle. The information gathered is used to diagnose neuromuscular disorders.

Muscular dystrophy—A group of inherited diseases characterized by progressive wasting of the muscles.

Sleep apnea—Temporary cessation of breathing while sleeping.

Trinucleotide repeat expansion—A sequence of three nucleotides that is repeated too many times in a section of a gene.

Genetic profile

The most common type of DM is called DM1 and is caused by a mutation in a **gene** called myotonic dystrophy protein kinase (DMPK). The DMPK gene is located on chromosome 19. When there is a mutation in this gene, a person develops DM1. The specific mutation that causes DM1 is called a trinucleotide repeat expansion.

Some families with symptoms of DM do not have a mutation in the DMPK gene. As of early 2001, scientists have found that the DM in many of these families is caused by a mutation in a gene on chromosome 3. However the specific gene and mutation have not yet been identified. These families are said to have DM2.

Trinucleotide repeats

In the DMPK gene, there is a section of the genetic code where the three letters CTG are repeated a certain number of times. In people who have DM1, this word is repeated too many times—more than the normal number of 37 times—and thus this section of the gene is too big. This enlarged section of the gene is called a trinucleotide repeat expansion.

People who have repeat numbers in the normal range will not develop DM1 and cannot pass it to their children. Having more than 50 repeats causes DM1. People who have 38–49 repeats have a premutation and will not develop DM1, but can pass DM1 onto their children. Having repeats numbers greater than 1,000 causes congenital myotonic dystrophy.

TABLE 1

Relationship between phenotype and CTG repeat length in myotonic dystrophy

Phenotype	Clinical signs	CTG repeat size	Age of onset (Years)	Average age of death (Years)
Premutation	None	38 to ~49	Normal	Normal
Mild	Cataracts mild myotonia	50 to ~150	20–70	60–normal
Classical	Weakness myotonia Cataracts Balding Cardiac arrhythmia Others	~100 to ~1000–1500	10–30	48–55
Congenital	Infantile hypotonia Respiratory deficits Mental retardation	~1000 to 2000	Birth to 10	45

In general, the more repeats in the affected range that someone has, the earlier the age of onset of symptoms and the more severe the symptoms. However, this is a general rule. It is not possible to look at a person's repeat number and predict at what age they will begin to have symptoms or how their condition will progress.

Exactly how the trinucleotide repeat expansion causes myotonia, the inability to relax muscles, is not yet understood. The disease somehow blocks the flow of electrical impulses across the muscle cell membrane. Without proper flow of charged particles, the muscle cannot return to its relaxed state after it has contracted.

Anticipation

Sometimes when a person who has repeat numbers in the affected or premutation range has children, the expansion grows larger. This is called anticipation. A larger expansion can result in an earlier age of onset in children than in their affected parent. Anticipation happens more often when a mother passes DM1 onto her children then when it is passed from the father. Occasionally repeat sizes stay the same or even get smaller when they are passed to a person's children.

Inheritance

DM is inherited through autosomal dominant **inheritance**. This means that equal numbers of males and females are affected. It also means that only one gene in the pair needs to have the mutation in order for a person to be affected. Since a person only passes one copy of each gene onto their children, there is a 50% or one in two chance that a person who has DM will pass it onto each of their children. This percentage is not changed by results of other pregnancies. A person with a premutation also has a 50%, or one in two, chance of passing the altered gene on to each of their children. However, whether or not their children will develop DM1 depends on whether the trinucleotide repeat becomes further expanded. A person who has repeat numbers in the normal range cannot pass DM1 onto their children.

Demographics

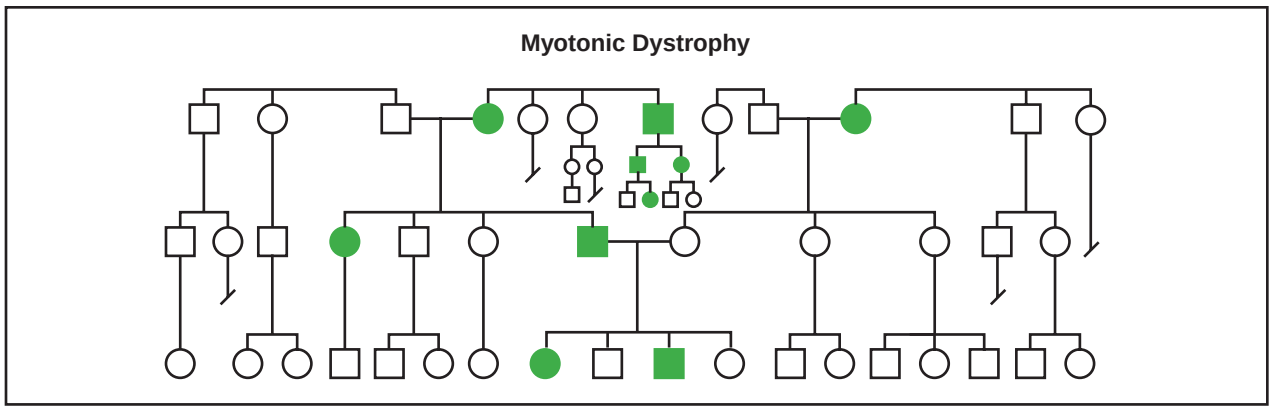
DM occurs in about one of 20,000 people and has been described in people from all over the world.

Signs and symptoms

There is a range in the severity of symptoms in DM and not everyone will have all of the symptoms listed here.

Myotonic dystrophy causes weakness and delayed muscle relaxation called myotonia. Symptoms of DM include facial weakness and a slack jaw, drooping eyelids called ptosis, and muscle wasting in the forearms and calves. A person with DM has difficulty relaxing his or her grasp, especially in the cold. DM affects the heart muscle, causing irregularities in the heartbeat. It also affects the muscles of the digestive system, causing constipation and other digestive problems. DM may cause cataracts, retinal degeneration, low IQ, frontal balding, skin disorders, atrophy of the testicles, and diabetes. It can also cause sleep apnea—a condition in which normal breathing is interrupted during sleep. DM increases the need for sleep and decreases motivation. Severe disabilities do not set in until about 20 years after symptoms begin. Most people with myotonic dystrophy maintain the ability to walk, even late in life.

A severe form of DM, congenital myotonic dystrophy, may appear in newborns of mothers who have DM1. Congenital myotonic dystrophy is marked by severe weakness, poor sucking and swallowing responses, respiratory difficulty, delayed motor development, and mental retardation. Death in infancy is common in this type.



(Gale Group)

Some people who have a trinucleotide repeat expansion in their DMPK gene do not have symptoms or have very mild symptoms that go unnoticed. It is not unusual for a woman to be diagnosed with DM after she has an infant with congenital myotonic dystrophy.

Predictive testing

It is possible to test someone who is at risk for developing DM1 before they are showing symptoms to see whether they inherited an expanded trinucleotide repeat. This is called predictive testing. Predictive testing cannot determine the age of onset that someone will begin to have symptoms, or the course of the disease.

Diagnosis

Diagnosis of DM is not difficult once the disease is considered. However, the true problem may be masked because symptoms can begin at any age, can be mild or severe, and can occur with a wide variety of associated complaints. Diagnosis of DM begins with a careful medical history and a thorough physical exam to determine the distribution of symptoms and to rule out other causes. A family history of DM or unexplained weakness helps to establish the diagnosis.

A definitive diagnosis of DM1 is done by **genetic testing**, usually by taking a small amount of blood. The **DNA** in the blood cells is examined and the number of repeats in the DMPK gene is determined. Various other tests may be done to help establish the diagnosis, but only rarely would other testing be needed. An electromyogram (EMG) is a test used to examine the response of the muscles to stimulation. Characteristic changes are seen in DM that helps distinguish it from other muscle diseases. Removing a small piece of muscle tissue for microscopic examination is called a muscle biopsy. DM is marked by characteristic changes in the structure of muscle cells that can be seen on a muscle biopsy. An electrocardiogram could be performed to detect characteristic abnormalities in heart rhythm associated with DM. These symptoms often appear later in the course of the disease.

Prenatal testing

Testing a pregnancy to determine whether an unborn child is affected is possible if genetic testing in a family has identified a DMPK mutation. This can be done at 10–12 weeks gestation by a procedure called chorionic villus sampling (CVS), which involves removing a tiny piece of the placenta and analyzing DNA from its cells. It can also be done by **amniocentesis** after 16 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it and those who are interested in learning more should check with their doctor or genetic counselor.

Another procedure, called preimplantation diagnosis allows a couple to have a child that is unaffected with the genetic condition in their family. This procedure is experimental and not widely available. Those interested in learning more about this procedure should check with their doctor or genetic counselor.

Treatment and management

Myotonic dystrophy cannot be cured, and no treatment can delay its progression. However, many of the symptoms it causes can be treated. Physical therapy can help preserve or increase strength and flexibility in muscles. Ankle and wrist braces can be used to support weakened limbs. Occupational therapy is used to develop tools and techniques to compensate for loss of strength and dexterity. A speech-language pathologist can provide retraining for weakness in the muscles controlling speech and swallowing.

Irregularities in the heartbeat may be treated with medication or a pacemaker. A yearly electrocardiogram is usually recommended to monitor the heartbeat. **Diabetes mellitus** in DM is treated in the same way that it is in the general population. A high-fiber diet can help prevent constipation. Sleep apnea may be treated with surgical procedures to open the airways or with nighttime ventilation. Treatment of sleep apnea may reduce drowsiness. Lens replacement surgery is available when cataracts develop. Pregnant woman should be followed by an obstetrician familiar with the particular problems of DM because complications can occur during pregnancy, labor, and delivery.

Wearing a medical bracelet is advisable. Some emergency medications may have dangerous effects on the heart rhythm in a person with DM. Adverse reactions to general anesthesia may also occur.

Prognosis

The course of myotonic dystrophy varies. When symptoms appear earlier in life, disability tends to become more severe. Occasionally people with DM may require a wheelchair later in life. Children with congenital DM usually require special educational programs and physical and occupational therapy. For both types of DM, respiratory infections pose a danger when weakness becomes severe.

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Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

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Karen M. Krajewski, MS, CGC

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Nail-patella syndrome

Definition

Nail-patella syndrome, is a genetic disease of the connective tissue that produces defects in the fingernails, knee caps, and kidneys.

Description

Nail-patella syndrome is also known as Fong Disease, Hereditary Onycho-Osteodysplasia (H.O.O.D.), Iliac Horn Disease, and Turner-Kieser syndrome. Patients who have nail-patella syndrome may show a variety of physical abnormalities. The hallmark features of this syndrome are poorly developed fingernails, toenails, and patellae (kneecaps). Other common abnormalities include elbow deformities, abnormally shaped pelvis bone (hip bone), and kidney (renal) disease.

Less common medical findings include changes in the upper lip, the roof of the mouth, and unusual skeletal abnormalities. Skeletal abnormalities may include poorly developed scapulae (shoulder blades), sideways bent fingers (clinodactyly), **clubfoot**, **scoliosis**, and unusual neck bones. There are also other effects, such as thickening of the basement membrane in the skin and of the tiny clusters of capillaries (glomeruli) in the kidney. Scientists have recognized an association between nail-patella syndrome and colon cancer. Nail-patella syndrome is associated with open-angle **glaucoma**, which, if untreated, may lead to blindness. Patients may also have cataracts, drooping eyelids (ptosis), or corneal problems such as glaucoma.

People with nail-patella syndrome may display only a few or many of the recognized signs of this disease. Symptoms vary widely from person to person. Signs even vary within a single family with multiple affected members.

Genetic profile

Nail-patella syndrome has been recognized as an inherited disorder for over 100 years. It is caused by mutations in a **gene** known as LIM Homeobox Transcription Factor 1-Beta (LMX1B), located on the long arm of chromosome 9.

The LMX1B gene codes for a protein that is important in organizing embryonic limb development. Mutations in this gene have been detected in many unrelated people with nail-patella syndrome. Scientists have also been able to interrupt this gene in mice to produce defects similar to those seen in human nail-patella syndrome.

Nail-patella syndrome is inherited in an autosomal dominant manner. This means that possession of only one copy of the defective gene is enough to cause disease. When a parent has nail-patella syndrome, each of their children has a 50% chance to inherit the disease-causing mutation.

A new mutation causing nail-patella syndrome can also occur in a person with no family history. This is called a sporadic occurrence and accounts for approximately 20% of cases of nail-patella syndrome. The children of a person with sporadic nail-patella syndrome are also at a 50% risk of developing signs of the disorder.

Demographics

The incidence of nail-patella syndrome is approximately one in 50,000 births. This disorder affects males and females equally. It is found throughout the world and occurs in all ethnic groups. The strongest risk factor for nail-patella syndrome is a family history of the disease.

Signs and symptoms

Medical signs of nail-patella syndrome vary widely between patients. Some patients with this disorder do not display symptoms. These patients are discovered to have the nail-patella syndrome only when genetic studies trace their family history. Scientists are now working to learn what causes different people to display such different symptoms of nail-patella syndrome.

KEY TERMS

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Glomeruli—Tiny clusters of capillaries in the kidney.

Hematuria—The presence of blood in the urine.

Patella—The kneecap.

Proteinuria—Excess protein in the urine.

The most obvious signs associated with nail-patella syndrome is absent, poorly developed, or unusual fingernails. Fingernail abnormalities are found in over 80% of patients with this disorder. Abnormalities may be found in one or more fingernails. Only rarely are all fingernails affected. This disease most commonly affects the fingernails of the thumbs and index fingers. The pinky fingernail is least likely to be affected. Fingernails may be small and concave with pitting, ridges, splits, and/or discoloration. Toenails are less often affected. The lunulae, or light-colored crescent moons, at the base of the fingernail bed next to the cuticle are sometimes triangularly-shaped in people with nail-patella syndrome.

Kneecap abnormalities are the second most common sign associated with this disorder. Either or both kneecaps may be missing or poorly formed. If present, kneecaps are likely to be dislocated. The knees of people with nail-patella syndrome may have a square appearance. Besides the kneecap, other support structures including bones, ligaments, and tendons may also be malformed. These support structures stabilize the knee, therefore patients with some leg malformations may have difficulty in walking.

The hip bones of approximately 80% of patients with nail-patella syndrome have unusual bony projections called posterior iliac horns. These bony projections, or spurs, are internal and not obvious unless they are detected on x ray. This unusual pelvic anatomy is not associated with any other disease.

Kidney disease is present in at least 30% of people with nail-patella syndrome. Biopsy shows lesions that resemble those of inflammation of the clusters of capillaries in the kidneys (glomerulonephritis), but without any infection present. Kidney failure is the most dangerous consequence of nail-patella syndrome. It occurs in about 30% of patients who have kidney involvement. An early sign of kidney involvement is the presence of protein or blood in the urine (chronic, benign proteinuria and hematuria). Kidney involvement is progressive, so early diagnosis and treatment of renal disease is important. Kidney disease has been reported in children with nail-patella syndrome, but renal involvement more commonly develops during adulthood.

Various skeletal symptoms may occur. Patients with nail-patella syndrome may not be able to fully straighten their arms at the elbow. This may create a webbed appearance at the elbow joint. Patients may have sideways bent fingers, poorly developed shoulder blades, clubfoot, hip dislocation, unusual neck bones, or scoliosis.

Eye problems may be present and vary from person to person. Nail-patella syndrome is associated with open angle glaucoma. Open angle glaucoma is caused by fluid blocked into the front chamber of the eye. This blocked fluid builds increasing pressure into the eye. If untreated, this increased pressure may lead to permanent damage of the optic nerve and irreversible blindness. Some patients with nail-patella syndrome have ptosis, or drooping eyelids. Nail-patella syndrome has also been associated with abnormalities of the cornea, cataracts, and astigmatism. Additionally, the irises of the eye may be multicolored, possibly displaying a clover-shaped pattern of color.

Diagnosis

As of early 2001, **genetic testing** for nail-patella syndrome is available only through research institutions that are working to further characterize this disorder. Genetic testing cannot predict which signs of the disease will develop. Nor can genetic testing predict the severity of disease symptoms. Improved genetic testing for nail-patella syndrome is anticipated in the future.

Diagnosis of this disease is most often made on visual medical clues such as the characteristic abnormalities of the fingernails and kneecaps. Diagnosis is confirmed by x ray images of the affected bones and, when indicated, kidney biopsy. The bony pelvic spurs found in 80% of patients with nail-patella syndrome are not associated with any other disease.

Prenatal diagnosis for nail-patella syndrome by third-trimester ultrasound was documented in 1998. Prenatal diagnosis via genetic testing of cells obtained by chorionic villus sampling was reported the same year. As of 2001, prenatal genetic testing for nail-patella syndrome is not yet widely available. There is controversy surrounding the use of prenatal testing for such a variable disorder. Prenatal testing cannot predict the extent of an individual's disease.

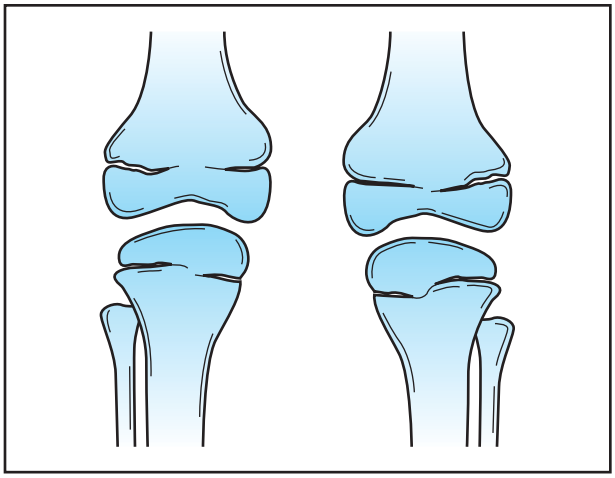

Diagram of two legs affected by nail-patella syndrome. Note the absence of the patella in this image of knees. *(Gale Group)*

Treatment and management

Treatment is usually not necessary. Treatment, when required, depends on each patient's specific symptoms. Severe kidney disease is treated with dialysis or a kidney transplant. Patients receiving kidney transplant do not develop nail-patella type renal complications in their new kidney.

A wheelchair may be required if walking becomes painful due to bone, tendon, ligament, or muscle defects. Orthopedic surgery may be necessary for congenital clubfoot deformity. Manipulation or surgery may be required to correct hip dislocation. Cataracts are also surgically treated. Medical treatment at early signs of glaucoma prevents progression of the disease to blindness.

Genetic counseling is offered to persons who have the disease. Parents with this disease have a 50% chance of passing it to each of their children. As of 2001, current genetic testing technology cannot predict the severity or scope of an individual's symptoms.

Because many possible manifestations of nail-patella syndrome exist, patients are advised to pursue extra medical care including regular urinalysis and special eye exams. Children with nail-patella syndrome should be screened for scoliosis.

Prognosis

Survival among patients with nail-patella syndrome is not decreased unless a they exhibit renal complications. It is estimated that 8% of individuals with nail-patella syndrome who seek medical attention eventually die of kidney disease.

Resources

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John Thomas Lohr
Judy C. Hawkins, MS

Naito-Oyanagi disease *see* **Dentatorubral-pallidoluysian atrophy**

Nanocephalic dwarfism *see* **Seckel syndrome**

Narcolepsy

Definition

Narcolepsy is a disorder marked by excessive daytime sleepiness, uncontrollable sleep attacks, and cataplexy (a sudden loss of muscle tone, usually lasting up to half an hour).

Description

Narcolepsy is the second-leading cause of excessive daytime sleepiness (after obstructive sleep apnea). Persistent sleepiness and sleep attacks are the hallmarks of this condition. The sleepiness has been compared to the feeling of trying to stay awake after not sleeping for two or three days.

People with narcolepsy fall asleep suddenly—anywhere, at any time, maybe even in the middle of a conversation. These sleep attacks can last from a few seconds to more than an hour. Depending on where they occur, they may be mildly inconvenient or even dangerous to the individual. Some people continue to function outwardly during the sleep episodes, such as talking or putting things away. But when they wake up, they have no memory of the event.

Narcolepsy is related to the deep, dreaming part of sleep known as rapid eye movement (REM) sleep. Normally when people fall asleep, they experience 90 minutes of non-REM sleep, which is then followed by REM sleep. People with narcolepsy, however, enter REM

KEY TERMS

Cataplexy—A symptom of narcolepsy in which there is a sudden episode of muscle weakness triggered by emotions. The muscle weakness may cause the person's knees to buckle, or the head to drop. In severe cases, the patient may become paralyzed for a few seconds to minutes.

Hypnagogic hallucinations—Dream-like auditory or visual hallucinations that occur while falling asleep.

Hypothalamus—A part of the forebrain that controls heartbeat, body temperature, thirst, hunger, body temperature and pressure, blood sugar levels, and other functions.

Sleep paralysis—An abnormal episode of sleep in which the patient cannot move for a few minutes, usually occurring on falling asleep or waking up. Often found in patients with narcolepsy.

sleep immediately. In addition, REM sleep occurs inappropriately throughout the day.

Genetic profile

In 1999, researchers identified the **gene** that causes narcolepsy. The gene allows cells in the hypothalamus (the part of the brain that regulates sleep behavior) to receive messages from other cells. When this gene is abnormal, cells cannot communicate properly, and abnormal sleeping patterns develop.

The disorder sometimes runs in families, but most people with narcolepsy have no relatives with the disorder. Researchers believe that the **inheritance** of narcolepsy is similar to that of heart disease. In heart disease, several genes play a role in being susceptible to the disorder, but it usually does not develop without an environmental trigger of some sort.

Demographics

There has been debate over the incidence of narcolepsy. It is thought to affect between one in every 1,000 to 2,000 Americans. The known prevalence in other countries varies, from one in 600 in Japan to one in 500,000 in Israel. Reasons for these differences are not clear.

Signs and symptoms

While the symptoms of narcolepsy usually appear during the teens or 20s, the disease may not be diagnosed for many years. Most often, the first symptom is an overwhelming feeling of fatigue. After several months or years, cataplexy and other symptoms appear.

Cataplexy is the most dramatic symptom of narcolepsy. It affects 75% of people with the disorder. During attacks, the knees buckle and the neck muscles go slack. In extreme cases, the person may become paralyzed and fall to the floor. This loss of muscle tone is temporary, lasting from a few seconds to half an hour, but frightening. The attacks can occur at any time but are often triggered by strong emotions, such as anger, joy, or surprise.

Other symptoms of narcolepsy include:

- Sleep attacks: short, uncontrollable sleep episodes throughout the day
- Sleep paralysis: a frightening inability to move shortly after awakening or dozing off
- Auditory or visual hallucinations: intense, sometimes terrifying experiences at the beginning or end of a sleep period
- Disturbed nighttime sleep: tossing and turning, nightmares, and frequent awakenings during the night

Diagnosis

If a person experiences both excessive daytime sleepiness and cataplexy, a diagnosis may be made on the patient history alone. Laboratory tests, however, can confirm a diagnosis. These may include an overnight polysomnogram—a test in which sleep is monitored with electrocardiography, video, and respiratory parameters. A Multiple Sleep Latency Test, which measures sleep latency (onset) and how quickly REM sleep occurs, may be used. People who have narcolepsy usually fall asleep in less than five minutes.

If a diagnosis is in question, a genetic blood test can reveal the existence of certain substances in people who have a tendency to develop narcolepsy. Positive test results suggest, but do not prove, the existence of narcolepsy.

Narcolepsy is a complex disorder, and it is often misdiagnosed. It takes 14 years, on average, for an individual to be correctly diagnosed.

Treatment and management

There is no cure for narcolepsy. It is not progressive, and it is not fatal, but it is chronic. The symptoms can be managed with medication or lifestyle adjustment. Amphetamine-like stimulant drugs are often prescribed to control drowsiness and sleep attacks. Patients who do

Narcolepsy causes affected individuals to suddenly fall into a deep sleep, even in the middle of an activity. *(Custom Medical Stock Photo, Inc.)*

not like taking high doses of stimulants may choose to take smaller doses and "manage" their lifestyles, such as by napping every couple of hours, to relieve daytime sleepiness. Antidepressants are often effective in treating symptoms of abnormal REM sleep.

With the recent discovery of the gene that causes narcolepsy, researchers are hopeful that therapies can be designed to relieve the symptoms of the disorder.

Prognosis

Narcolepsy is not a degenerative disease, and patients do not develop other neurologic symptoms. However, narcolepsy can interfere with a person's ability to work, play, drive, and perform other daily activities. In severe cases, the disorder prevents people from living a normal life, leading to **depression** and a loss of independence.

Resources

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ORGANIZATIONS

American Sleep Disorders Association. 1610 14th St. NW, Suite 300, Rochester, MN 55901. (507) 287-6006.

Narcolepsy Network. PO Box 42460, Cincinnati, OH 45242. (973) 276- 0115.

National Center on Sleep Disorders Research. Two Rockledge Centre, 6701 Rockledge Dr., Bethesda, MD 20892. (301) 435-0199.

National Sleep Foundation. 1367 Connecticut Ave. NW, Suite 200, Washington, DC 20036. (202) 785-2300.

Stanford Center for Narcolepsy. 1201 Welch Rd-Rm P-112, Stanford, CA 94305. (415) 725-6517.

University of Illinois Center for Narcolepsy Research. 845 S. Damen Ave., Chicago, IL 60612. (312) 996-5176.

WEBSITES

"Stanford Researchers Nab Narcolepsy Gene For Sleep Disorders." *Stanford University Medical Center*. [August 5, 1999]. <http://www.stanford.edu/%7Edement/ngene.html>.

Michelle Lee Brandt

Nephrogenic diabetes insipidus

Definition

Nephrogenic diabetes insipidus (NDI) is a kidney disorder characterized by the organ's inability to respond to the antidiuretic hormone (ADH), also called arginine vasopressin (AVP), produced in the hypothalamus, a structure of the brain. NDI involves an abnormality in the kidney tubules which prevents the proper amount of water from being reabsorbed from the kidneys back into the body. Instead, the water is excreted in large amounts as diluted urine.

Description

There are two categories of nephrogenic diabetes insipidus: inherited and acquired. Within the inherited group, there are three types of NDI: X-linked, autosomal recessive, and autosomal dominant. Unlike the more common diabetic disorder **diabetes mellitus**, NDI is not

related to insulin production or levels of sugar in the blood and urine.

Ninety percent of inherited NDI is X-linked, meaning it is caused by an alteration in a **gene** carried on the X chromosome. Since women have two X **chromosomes** and men have only one, an X-linked recessive condition is expected to effect men since they do not have a second X chromosome with a normal copy of the gene to produce the needed substance. Autosomal recessive NDI is rarer and equally affects males and females. Autosomal dominant NDI is the most rare of the three and affects both males and females.

Inherited NDI is present from birth and symptoms usually manifest within the first several days of life. If the disorder is not diagnosed and treated early, it will cause the body to lose too much water. This dehydration can lead to brain damage and eventually death. But, with early diagnosis and treatment to avoid severe dehydration, the person can live a normal life span without any mental impairment.

Acquired NDI is the most common type of the disease and can be acquired at any age. It is most frequently acquired through the long-term use of certain prescription medicine, including demeclocycline, methicillin, foscarnet, and some anticancer drugs. In rare instances, it can be caused by an underlying disease or disorder, such as **sickle cell anemia**, chronic kidney failure, sarcoidosis, amyloidosis, Fanconi syndrome, and Sjögrens syndrome. Other rare causes of acquired NDI are low blood levels of potassium and abnormally high blood calcium levels. Pregnancy can also result in temporary acquired NDI. However, most cases of acquired NDI are caused by long-term use of the prescription drug lithium, used to treat **bipolar disorder** (manic **depression**).

NDI, also called gypsy's curse, is caused by the kidneys inability to respond to the water-saving hormone (ADH), a natural chemical manufactured in the brain but works in the kidneys. The body's two kidneys make urine, which is then sent to the bladder, and help to maintain the balance of water, salt, and minerals. A majority of the water is reabsorbed from nephrons in the kidneys into surrounding inner tissue. Each kidney contains hundreds of thousands of nephrons, microscopic-size tubes that filter the water flowing into the kidneys. The water that is not absorbed becomes urine.

The first references to NDI appeared in medical literature in the 1880s, but it wasn't until the 1940s that detailed observations and studies were done. In a landmark 1946 study published in the *American Journal of the Diseases of Children*, authors A. J. Waring, L. Kajdi, and V. Tappan, summarized the main clinical and pathophysiological aspects of the disorder. "The presenting complaints were unexplained fever, failure to gain weight, and constipation. The bouts of dehydration are usually not associated with acidosis. The thirst of one of the patients studied was satisfied only when five to six times the normal requirement of fluid was offered. The levels of (blood) serum sodium and chloride decreased to normal and the infant remained free from fever on this high fluid intake."

Genetic profile

Genes are the blueprint for the human body that directs the development of cells and tissue. Mutations in some genes can cause **genetic disorders** such as inherited nephrogenic diabetes insipidus. Every cell in the body has 23 pairs of chromosomes, 22 pairs of which are called autosomes and contain two copies of individual genes. The 23rd pair of chromosomes is called the sex chromosome because it determines a person's sex. Men have an X and a Y chromosome while women have two X chromosomes. X-linked nephrogenic diabetes insipidus is caused by a defect in the vasopressin-2 receptor (AVPR2) gene in the X chromosome which renders the kidneys unreceptive to ADH.

Since inherited NDI is usually inherited as an X-linked condition, almost all persons with the disorder are male. Females have two X chromosomes, which means they have two copies of each gene. Males have only one X chromosome and one copy of each gene. If a male has an altered AVPR2 gene, he will have NDI. If a female has one altered gene, she will be a carrier and will be at risk to pass the altered gene on to her children. If her son inherits the altered gene, he will be affected. If her daughter inherits the affected gene, she will be a carrier like her mother. If her son does not inherit the altered gene, he will not be affected and will not pass the altered gene on to his children. If a daughter does not inherit the altered gene, she will not pass it on to her children. If an affected male has children, all of his daughters will be carriers but none of his sons will be affected.

Women who have the abnormal AVPR2 gene may have milder symptoms of NDI than males. This is because early in development, one X-chromosome in each cell of a female is "turned off" at random. If by chance a woman has more than half of the X chromosomes that carry the normal AVPR2 gene turned off, she may have mild symptoms of NDI. Approximately 90% of people with inherited NDI have it as a result of this X-linked gene.

The gene that produces aquaporin-2 (AQP2) can cause autosomal recessive and autosomal dominant NDI when altered. The AQP2 gene produces a protein that helps the kidneys reabsorb water into the body and con-

centrate urine. Since the AQP2 gene is carried on chromosome 12, a non-sex chromosome, it is carried in both males and females. Also, an abnormal AQP2 gene is recessive, meaning if only one of the person's two AQP2 genes is abnormal, it will not cause NDI. If both genes are abnormal, then that person will have NDI. A child born to a couple who are both carriers of autosomal recessive NDI has a 25% chance to be affected since the child is at risk to receive a copy of the altered gene from its mother and father. In autosomal dominant NDI, either parent may be affected and may pass the altered gene to the child. Also, only one altered gene is necessary to be present for the condition to manifest. Acquired NDI is not hereditary and can not be genetically passed on from parents to their offspring.

Demographics

In general, the various types of NDI appear to affect people regardless of age, race, or ethnicity. However, in X-linked NDI, the predominance of cases is among males. The exact number of people with NDI is not known. Estimates range from one in every 500,000 to five in every 100,000. In acquired NDI, one of the diseases that can cause it is sickle cell anemia, which occurs primarily in people of African descent.

Signs and symptoms

The primary symptoms for all types of NDI are generally the same: polyuria (excreting large amounts of dilute urine), and polydipsia, drinking excessive amounts of water, from 3-10 gal (12-38 L) per day. In infants born with NDI, symptoms begin to occur within a few days after birth. But since a child cannot verbally communicate its need for larger than normal amounts of water, parents, physicians, and other caregivers must be alert to other signs of the disorder. Overt signs include fever, irritability, and constipation, all of which may indicate dehydration. The child may also vomit often, be anorexic, and prefer water to milk. Other signs include rapid and severe dehydration if fluids are restricted or withheld, high levels of sodium and chloride in the blood, and urine that does not have a high specific gravity.

Elderly people, usually those with acquired NDI, may need close monitoring for symptoms especially if they are unable to communicate their need for lots of water, such as patients with **Alzheimer disease** or other mental deterioration. Also, elderly persons may be less sensitive to their need for water. Because of this, elderly persons with NDI can be more prone to dehydration, leading to such problems as infection, kidney failure, confusion, lethargy, and constipation.

KEY TERMS

Acidosis—A condition of decreased alkalinity resulting from abnormally high acid levels (low pH) in the blood and tissues. Usually indicated by sickly sweet breath, headaches, nausea, vomiting, and visual impairments.

Alzheimer disease—A degenerative disease of the central nervous system characterized by premature senility and other mental deterioration.

Amyloidosis—Accumulation of amyloid deposits in various organs and tissues in the body such that normal functioning of an organ is compromised.

Dehydration—An extreme loss of water in the body which, if untreated, can lead to brain damage and death.

Electrolyte—A solution or a substance in a solution consisting of various chemicals that can carry electric charges. They exist in the blood as acids, bases, and salts, such as sodium, calcium, potassium, chlorine, and magnesium.

Fanconi syndrome—A reabsorbtion disorder in the kidney tubules.

Kidney tubules—A portion of the kidneys that causes water to be excreted as urine or reabsorbed into the body.

Nephrons—Microscopic-size tubes that filter the water that flows into the kidneys.

Osmolarity—The concentration of an osmotic solution, especially when measured in osmols or milliosmols per liter of solution.

Osmotically—Referring to the movement of a solvent through a semipermeable membrane (as of a living cell) into a solution of higher solute concentration that tends to equalize the concentrations of solute on the two sides of the membrane.

Sarcoidosis—A chronic disease characterized by nodules forming in the lymph nodes, lungs, bones, and skin.

Sickle cell anemia—A chronic, inherited blood disorder characterized by sickle-shaped red blood cells. It occurs primarily in people of African descent, and produces symptoms including episodic pain in the joints, fever, leg ulcers, and jaundice.

Sjogren syndrome—A chronic inflammatory disease often associated with rheumatoid arthritis.

For acquired NDI, close medical monitoring should be done for people at high risk for the disorder. These include people undergoing long-term treatment with lithium, and people with sickle cell anemia, chronic kidney failure, other kidney problems, very low blood levels of potassium and protein, and high blood levels of calcium.

Diagnosis

NDI is one of four types of diabetes insipidus (DI). In all four types, the basic symptoms are extreme thirst and excessive urination. Depending on other symptoms and conditions present in the patient, it can often be easy for a physician to suspect NDI. But additional tests are required to confirm it. These include a test of urine concentration to measure the ratio of osmotically active particles (such as sodium) to body water, a blood test to determine plasma concentrations, measuring urine volume, and a test to determine the level of the antidiuretic hormone AVP in blood plasma.

Sometimes physicians will have the patient take a water deprivation test to help determine the type of NDI present. In this test, the patient goes without water or other liquids for up to six hours. The blood plasma concentrations and urine volume are then measured. Even though a patient with NDI will become dehydrated during this test, the doctor monitors the patient's body weight and blood plasma osmolarity levels to insure they remain within safe parameters. At the end of the test, the patient is generally diagnosed with NDI if he or she has high levels of osmotically active particles in the blood and low levels of osmotically active particles in the urine.

The patient is also given desmopressin acetate (DDAVP), a synthetic version of AVP, to determine if the patient has a different form of DI called pituitary diabetes insipidus, also known as central diabetes insipidus. In addition, the physician measures heart rate and diastolic blood pressure to help determine whether the NDI is caused by defective AVPR2 genes or defective AQP2 genes.

Treatment and management

Although there is no cure for NDI, all forms of the disorder are treatable. Drinking plenty of water is the first and foremost treatment. Regardless of age of the patient, water must be available at all times. However, it is important for a child to maintain control of their NDI with medication so that they can eat, drink, and grow normally.

Medications used to treat NDI include one or a combination of indomethacin (Indocin), amiloride (Midamor), the thiazide diuretics hydrochlorothiazide (Hydrodiuril) or Chlorothiazide (Diuril), and occasionally desmopressin.

Management of NDI is also accomplished through restricting the intake of sodium and sometimes protein. Thiazide diuretics can reduce a patient's urine output, but they may also cause potassium depletion. Potassium supplements may be required. NDI that occurs during pregnancy usually goes away after delivery of the child. NDI caused by diet abnormalities are usually reversible once the diet becomes balanced. Acquired NDI caused by electrolyte imbalances such as low levels of calcium in the blood plasma or high levels of potassium in the blood plasma can be reversed once the imbalance is corrected.

In patients with lithium-induced NDI, thiazide diuretics are used cautiously since they reduce the kidneys' ability to excrete lithium. In many, but not all cases, people with lithium-induced NDI can improve when the dosage is decreased or stopped. In some cases, the lithium-induced NDI is irreversible.

Prognosis

Infants and children with inherited NDI can live a normal life span providing they are diagnosed correctly, treated early, and properly manage the disorder. Without early diagnosis and treatment in infancy, NDI can lead to mental retardation and even death. Infants and children with NDI tend to be slightly smaller and weigh less than children without NDI. As children with NDI mature into adults, they tend to be slightly shorter than their parents, but with a normal weight. With appropriate treatment and management, NDI should not interfere with activities such as school, work, or sports.

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ORGANIZATIONS

Nephrogenic Diabetes Insipidus Foundation. PO Box 1390, Eastsound, WA 98245. (888) 376-6343. Fax: (888) 376-3842. <http://www. Ndi.org>.

WEBSITES

Diabetes Insipidus Foundation. <http://diabetesinsipidus.maxinter.net>.

Ken R. Wells

Neu-Laxova syndrome

Definition

Neu-Laxova syndrome is a rare disorder characterized by onset of severe growth delay during pregnancy, multiple birth defects, and abnormal physical development of the brain. Affected infants typically die shortly after delivery or are stillborn.

Description

In 1971, Dr. Neu published the first report of a family that included three children with a unique pattern of multiple birth defects. Each child had an unusually small head (*microcephaly*) and abnormalities of their arms, legs, skin, and external genitalia. The two affected daughters were each stillborn, while the affected son only lived for seven weeks. In 1972, Dr. Laxova described a different family whose children had birth defects similar to those first described by Dr. Neu. The parents in this second family were first cousins to one another. Taken together, these two families were considered evidence of a previously unrecognized genetic syndrome. The disorder was named Neu-Laxova syndrome in honor of these two physicians.

Neu-Laxova syndrome (NLS) has since become known as a rare, lethal inherited condition characterized by a specific pattern of facial, brain, and limb abnormalities. Other associated abnormalities often include dry, scaly skin, generalized swelling of body tissues (edema), and extremely slow growth.

Genetic profile

Neu-Laxova syndrome is inherited as an autosomal recessive condition. Males and females are equally likely to be affected. It has been reported in a variety of ethnic groups. Proof of autosomal recessive **inheritance** includes the birth of more than one affected child to normal parents, and the observed incidence of infants with NLS among the children of two blood relatives. Consanguinity, or the mating of two biologically related individuals, increases the possibility of having a child with a genetic disorder. Since any two relatives will share a portion of their genes in common, they are more likely to each be a carrier of the same autosomal recessive **gene**.

In order to be affected with NLS, an individual must inherit two copies of the NLS gene, or one copy from each carrier parent. A carrier has one NLS gene and one normal gene; as such, a NLS carrier appears completely normal. However, two carriers face a risk of 25%, or a one in four chance, of having a child with NLS. Conversely, they also have a 75% chance of having an unaffected child. These risks apply to each of their pregnancies together.

Infants with NLS have also been born to non-consanguineous, or unrelated, couples. Anytime a child with NLS is born, the parents must be obligate, or mandatory, carriers of one NLS gene. As such, they face an increased risk in future pregnancies together of having another affected child.

The gene for NLS has not yet been identified. Thus, it is not possible to perform direct **genetic testing** to determine carrier status, confirm a clinical diagnosis, or provide accurate prenatal diagnosis.

Demographics

Adequate data are not available to provide a specific statistic regarding the frequency of NLS. The condition is very rare. According to a 1995 publication, only 40 cases of Neu-Laxova syndrome had been reported up to that point in medical literature.

Signs and symptoms

Stillborn or newborn infants with NLS have a characteristic pattern of internal and external abnormalities. Not all affected infants will have all of the features listed below, and some anomalies are slightly more common than others.

Infants with Neu-Laxova syndrome often have unusual facial features. Their heads are very small, and their foreheads appear to slant backwards. The distance between the eyes is wider than normal (*hypertelorism*),

KEY TERMS

Agenesis of the corpus callosum—Failure of the corpus callosum to form and develop. The corpus callosum is the band of nerve fibers located between the two sides, or hemispheres, of the brain.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

Cerebellum—A portion of the brain consisting of two cerebellar hemispheres connected by a narrow vermis. The cerebellum is involved in control of skeletal muscles and plays an important role in the coordination of voluntary muscle movement. It interrelates with other areas of the brain to facilitate a variety of movements, including maintaining proper posture and balance, walking, running, and fine motor skills, such as writing, dressing, and eating.

Cleft lip—A separation of the upper lip that is present from birth but originates early in fetal development. A cleft lip may appear on one side (unilateral) or both sides (bilateral) and is occasionally accompanied by a cleft palate. Surgery is needed to completely repair cleft lip.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Dandy-Walker malformation—A complex structural abnormality of the brain frequently associated with hydrocephalus, or accumulation of excess fluid in the brain. Abnormalities in other areas of the body may also be present. Individuals with Dandy-Walker malformation have varying degrees of mental handicap or none at all.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Stillbirth—The birth of a baby who has died sometime during the pregnancy or delivery.

and the eyes are prominent or bulging. Cataracts may be present. The eyelids are typically absent. The bridge of the nose is wide and slightly flattened. The ears are abnormally shaped. The lower jaw appears recessed as compared to the upper jaw (*retrognathia*), and the mouth itself is usually open with abnormally thick lips. Cleft lip may be present, with or without cleft palate.

The external features of the head and face are a reflection of severe physical abnormalities of the brain. It is not unusual for an infant with NLS to have an underdeveloped cerebellum or even lissencephaly, a more serious malformation characterized by a smooth brain surface. Normal development of the brain includes an intricate pattern of grooves, or gyri, on its outer surface. A lack of these grooves leads to profound mental retardation among survivors and an increased frequency of medical complications, such as seizures. Other reported brain malformations include agenesis of the corpus callosum and **Dandy-Walker malformation**.

A variety of limb abnormalities have also been described in NLS. Affected individuals often have shortened arms and legs that are held out from the body in an unusual, fixed position. This positioning is often referred to as flexion contractures. The fingers and toes may appear underdeveloped (*hypoplastic*) and/or fused together (*syndactyly*). The heels of the feet are often rounded (*rocker-bottom feet*), and the neck is short.

Other abnormalities more common to NLS include markedly limited physical growth. This typically begins during pregnancy and, as such, is referred to as intrauterine growth restriction (IUGR). Edema, or an excessive amount of fluid in the tissues of the body, is a hallmark of NLS. The edema may either be generalized and very severe throughout the body or limited only to the face or scalp. The skin is often extremely dry and scaly, a medical condition called ichthyosis. The lungs are often hypoplastic (underdeveloped), even when delivery occurs at term. The external genitalia are often abnormal, but this is more obvious in males than in females since males typically have a small, underdeveloped penis.

Finally, in addition to IUGR during pregnancy, an excessive volume of amniotic fluid (*polyhydramnios*) often develops. This is due to a combination of abnormal fluid production and impaired fetal swallowing from the associated nervous system abnormalities. The placenta is also usually abnormal in appearance and function.

Diagnosis

Many infants with NLS have been born into families with no previous history of the disorder and/or ones in which the parents are unrelated. Thus, an exact diagnosis of NLS during pregnancy may be very difficult, particularly for a couple with no apparent risk factors. Direct genetic testing for NLS will not be possible until the responsible gene has been identified. Some non-specific prenatal findings should, however, alert the physician that additional prenatal evaluation is warranted. These

include IUGR and polyhydramnios. Both findings often lead to an obvious difference in the size of a pregnant woman's uterus and her estimated weeks of pregnancy. A woman whose fetus has severe IUGR and normal amniotic fluid, often appears less pregnant than she actually is. In contrast, a woman with polyhydramnios often appears more pregnant, or larger. A detailed prenatal ultrasound test may be used to obtain pictures of abnormalities of the fetus as well as possible abnormalities of the placenta whenever there is an apparent discrepancy in a woman's size and her dates.

Two groups have separately reported diagnosis of NLS using ultrasound. However, in both cases, the diagnosis was formally established only after delivery. A number of the physical findings associated with NLS, particularly those involving the face, limbs, and brain, may be apparent following a detailed ultrasound later in pregnancy. In experienced hands and with the knowledge of a previous affected infant, some of these findings may be observed earlier.

In one of the published cases, a diagnosis of NLS was helped by the physical findings of an ultrasound exam at 32 weeks of pregnancy. The fetus was found to have many of the abnormalities associated with NLS. In the second report, ultrasound was used to assess fetal movement patterns at 34 weeks of pregnancy. Abnormal fetal movement is indicative of abnormal brain development. The authors were able to document a lack of normal fetal activity, such as breathing movements, sucking, swallowing, hiccups, and movements of the arms and legs in a fetus diagnosed with NLS after birth.

Accurate diagnosis of this condition is difficult before birth for those couples in which no NLS gene has been identified and no family history of NLS is known. While the combination of abnormal physical development and possibly abnormal fetal activity is highly indicative of a severe genetic condition, both would not be specific enough to pinpoint Neu-Laxova syndrome as the cause in all cases. Other genetic syndromes would be under consideration, pending a clinical examination after delivery.

For this reason, a careful physical evaluation after birth is critical in establishing a diagnosis of NLS. For those infants who are stillborn and for those who die after delivery, an autopsy is also helpful in documenting all of the associated internal abnormalities. A precise diagnosis facilitates accurate **genetic counseling**, including prognosis for an affected child and the risk of recurrence for future pregnancies.

Treatment and management

For those couples who have had a previous child with Neu-Laxova syndrome, serial prenatal ultrasound evaluations should be offered to monitor fetal growth, screen for physical abnormalities, and, assess fetal well-being later in pregnancy given the increased risk for stillbirth. Ultrasound diagnosis of any of the structural birth defects associated with NLS in these families should be considered evidence of the disorder. Since some of these findings may not become evident until later in pregnancy, termination of the pregnancy may not be an option for some couples. Plans for the remainder of the pregnancy as well as delivery can, however, be discussed. Given the serious prognosis associated with NLS, some parents may find a non-interventionist approach during labor and delivery, such as no fetal monitoring or Cesarean section delivery, acceptable. A clinical examination after birth is recommended.

Most infants with NLS have either been stillborn or died very shortly after delivery. However, there is one reported case of an affected Japanese infant who lived for 134 days. Humane medical care is therefore appropriate in survivors although the prognosis would still be extremely poor.

An autopsy is recommended on all affected infants after death to document and confirm all of the associated physical abnormalities. While this acts as a way to confirm the diagnosis, it is also a useful way to continue to add to the knowledge about the syndrome and its physical effects.

Prognosis

The number of infants described with Neu-Laxova syndrome is small. However, with the exception of the reported infant who lived 134 days, all affected children have either died before delivery or shortly thereafter. Neu-Laxova syndrome is a serious genetic condition whose anomalies prevent long-term survival.

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ORGANIZATIONS

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Helpline) or (202)

966-5557. Fax: (888) 394-3937 info@geneticalliance. <http://www.geneticalliance.org>.

Lissencephaly Network, Inc. 716 Autumn Ridge Lane, Fort Wayne, IN 46804-6402. (219) 432-4310. Fax: (219) 432-4310. lissennet@lissencephaly.org. <http://www.lissencephaly.org>.

WEBSITES

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"OMIM—Online Mendelian Inheritance in Man." <http://www.ncbi.nlm.nih.gov/omim>.

Terri A. Knutel, MS, CGC

KEY TERMS

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Meninges—The two-layered membrane that covers the brain and spinal cord.

Neural tube defect *see* **Spina bifida**

Neural tube defects

Definition

Neural tube defects are a group of severe birth defects in which the brain and spinal cord are malformed and lack the protective skeletal and soft tissue encasement.

Description

Incomplete formation and protection of the brain or spinal cord with bony and soft tissue coverings during the fourth week of embryo formation are known collectively as neural tube defects. Lesions may occur anywhere in the midline of the head or spine. These defects are among the most common serious birth defects, but they vary considerably in their severity. In some cases, the brain or spinal cord is completely exposed, in some cases protected by a tough membrane (meninges), and in other cases covered by skin.

Spina bifida accounts for about two-thirds of all neural tube defects. The spine defect may appear anywhere from the neck to the buttocks. In its most severe form, termed "spinal rachischisis," the entire spinal canal is open exposing the spinal cord and nerves. More commonly, the defect appears as a localized mass on the back that is covered by skin or by the meninges.

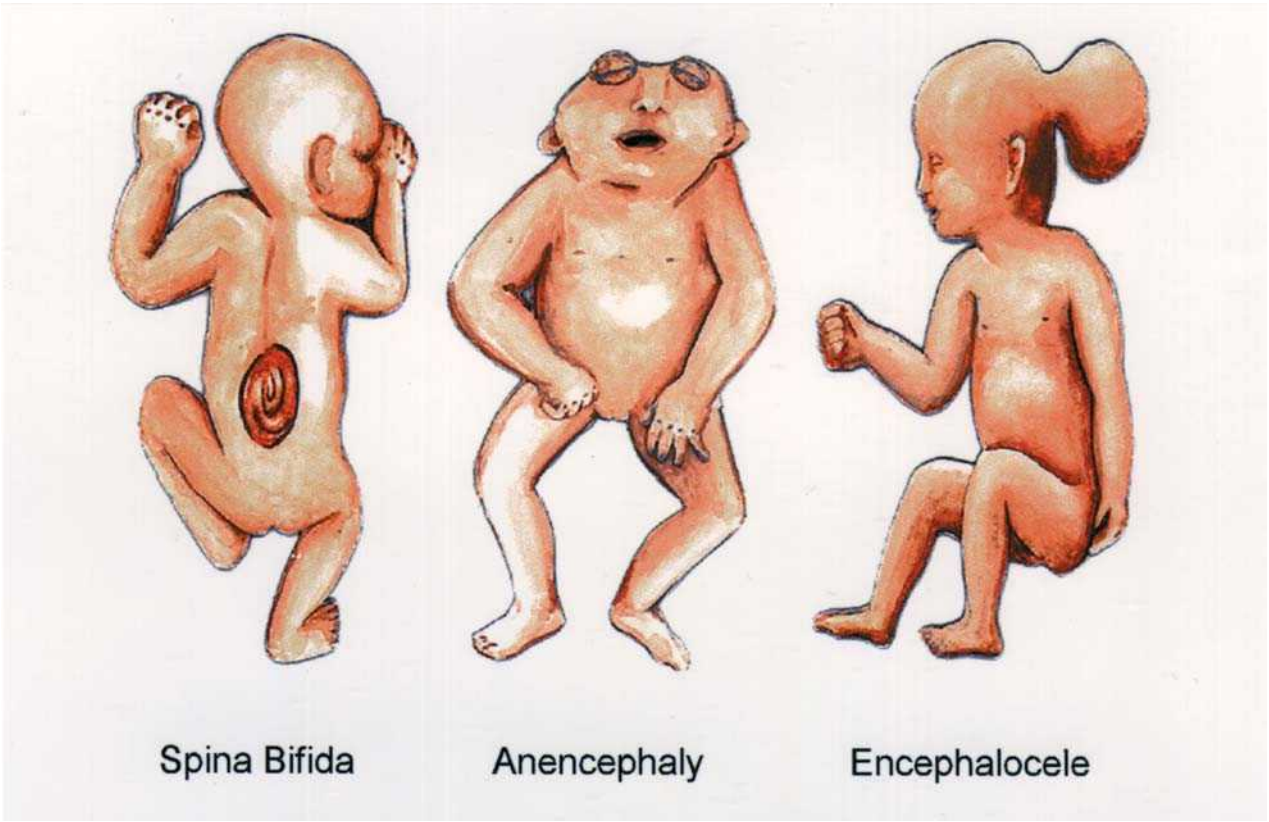
Anencephaly, the second most common neural tube defect, accounts for about one-third of cases. Two major subtypes occur. In the most severe form, all of the skull bones are missing and the brain is exposed in its entirety. The second form, in which only a part of the skull is missing and a portion of the brain exposed, is termed "meroacrania."

Encephaloceles are the least common form of neural tube defects, comprising less than ten percent of birth defects. With encephaloceles, a portion of the skull bones are missing leaving a bony hole through which the brain and its coverings herniate (protrude). Encephaloceles occur in the midline from the base of the nose, to the junction of the skull and neck. As with spina bifida, the severity varies greatly. In its mildest form, encephaloceles may appear as only a small area of faulty skin development with or without any underlying skull defect. At the severe end of the spectrum, most of the brain may be herniated outside of the skull into a skin-covered sac.

Genetic profile

Most neural tube defects (80-90%) occur as isolated defects. Neural tube defects of this variety are believed to arise through the combined influence of genetic and environmental forces. This multifactorial causation presumes that one or more predisposing genes collaborate with one or more environmental influences to lead to the birth defect. Poor nutrition is believed to be an environmental risk factor and hereditary defects in the absorption and utilization of folic acid are presumptive genetic predisposing factors. After a couple has one infant with a neural tube defect, the recurrence risk is 3-5%. After the birth of two NTD-affected infants, the risk increases to 8-10%.

When neural tube defects occur concurrently with other malformations there is a greater likelihood of an underlying specific genetic or environmental cause. Genetic causes include chromosome aberrations and single gene mutations. Environmental causes include maternal **diabetes mellitus**, exposure to prolonged hyperthermia, and seizure medications during the early months of pregnancy.



This illustration depicts three common neural tube defects. Spina bifida appears as a localized mass on the back covered by skin or by the meninges, the three-layered membrane that envelops the spinal cord. Anencephaly is a lethal birth defect characterized by absence of all or part of the skull and scalp and malformation of the brain. Encephaloceles are rare and are characterized by protrusion of brain tissue and membranes through the skull. *(Greenwood Genetic Center)*

Demographics

Neural tube defects occur worldwide. It appears that the highest prevalence (about one in 100 pregnancies) exists in certain northern provinces in China; an intermediate prevalence (about one in 300-500 pregnancies) has been found in Ireland and in Central and South America; and the lowest prevalence (less than one in 2,000 pregnancies) has been found in the Scandinavian countries. In the United States, the highest prevalence has occurred in the Southeast. Worldwide there has been a steady downward trend in prevalence rates over the past 50-70 years.

Signs and symptoms

Because of the faulty development of the spinal cord and nerves, a number of consequences are commonly seen in spina bifida. As a rule, the nerves below the level of the defect develop in a faulty manner and fail to function, resulting in paralysis and loss of sensation below the level of the spinal lesion. Since most defects occur in the lumbar region, the lower limbs are usually paralyzed and lack normal sensation. Furthermore, the bowel and bladder have inadequate nerve connections, causing inability to control bladder and bowel function. Sexual function is likewise impaired. Hydrocephaly develops in most infants either before or after surgical repair of the spine defect.

In anencephaly, the brain is destroyed by exposure during intrauterine life. Most infants with anencephaly are stillborn, or die within the initial days or weeks after birth.

Infants with encephaloceles have variable neurologic impairments depending on the extent of brain involvement. When only the brain covering is involved, the individual may escape any adverse effect. However, when the brain is involved in the defect, impairments of the special senses such as sight, hearing, and cognitive thinking commonly result.

Diagnosis

At birth, the diagnosis is usually obvious based on external findings. Prenatal diagnosis may be made with ultrasound examination after 12-14 weeks of pregnancy.

Screening of pregnancies can be carried out at 16 weeks by testing the mother's blood for the level of alpha-fetoprotein. Open neural tube defects leak this fetal chemical into the surrounding amniotic fluid, a small portion of which is absorbed into the mother's blood.

Treatment and management

No treatment is available for anencephaly. Aggressive surgical and medical management has improved survival and function of infants with spina bifida. Surgery closes the defect, providing protection against injury and infection. A common complication that may occur before or after surgical correction is the accumulation of excessive cerebral spinal fluid (hydrocephaly) in the major cavities (ventricles) within the brain. Hydrocephaly is usually treated with the placement of a mechanical shunt, which allows the cerebral spinal fluid from the ventricles to drain into the circulation or another body cavity. A number of medical and surgical procedures have been used to protect the urinary system as well. Walking may be achieved with orthopedic devices. Encephaloceles are usually repaired by surgery soon after birth. The success of surgery often depends on the amount of brain tissue involved in the **encephalocele**.

It has been found that 400 micrograms of folic acid taken during the periconceptional period (two to three months prior to conception, and two to three months following conceptions) protects against most neural tube defects. While there are a number of foods (green leafy vegetables, legumes, liver, and orange juice) that are good sources of natural folic acid, synthetic folic acid is available in over-the-counter multivitamins and a number of fully-fortified breakfast cereals.

Additionally, a population-wide increase in folic acid intake has been achieved through the fortification of enriched cereal grain flours since January 1998, a measure authorized by the United States Food and Drug Administration. The increased blood folic acid levels achieved in recent years has likely resulted from the synergy of dietary, supplementation, and fortification sources of folic acid.

Prognosis

Infants with anencephaly are usually stillborn or die within the initial days of life. Eighty to ninety percent of infants with spina bifida survive with surgery. Paralysis below the level of the defect, including an inability to control bowel and bladder function, and hydrocephaly are complications experienced by most survivors. Intellectual function is normal in most cases.

The prognosis for infants with encephaloceles varies considerably. Small encephaloceles may cause no disability whether surgical correction is performed or not. Infants with larger encephaloceles may have residual impairment of vision, hearing, nerve function, and intellectual capacity.

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ORGANIZATIONS

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Birth Defects Prevention Network. Atlanta, GA (770) 488-3550. <http://www.nbdpn.org>.

Shriners Hospitals for Children. International Shrine Headquarters, 2900 Rocky Point Dr., Tampa, FL 33607-1460. (813) 281-0300.

Spina Bifida Association of America. 4590 MacArthur Blvd. NW, Suite 250, Washington, DC 20007-4226. (800) 621-3141 or (202) 944-3285. Fax: (202) 944-3295.

Roger E. Stevenson, MD

Neuraminidase deficiency

Definition

Neuraminidase deficiency, or sialidosis, is a rare inherited metabolic disorder with multiple symptoms that can include skeletal abnormalities and progressive neurological degeneration.

Description

Nomenclature

Neuraminidase deficiency is caused by a mutation, or change, in the NEU1 **gene** that codes for the lysosomal enzyme alpha-N-acetylneuraminidase, or neuraminidase for short. This enzyme sometimes is referred to as sialidase. It is also sometimes called N-acetyl-neuraminic acid hydrolase. The disorder is manifested in one of two forms, known as sialidosis types I and II. Sialidosis type I is the milder form of the disorder, with symptoms typically appearing during adolescence. It is known as the non-dysmorphic or normophormic form of sialidosis. Sialidosis type II is the more severe form of

neuraminidase deficiency, with symptoms developing in the fetus, at birth, or during infancy or early childhood. It is known as the dysmorphic form of sialidosis.

Over the years, this disorder has been called by a number of different names, in addition to neuraminidase deficiency, alpha-neuraminidase deficiency, sialidase deficiency, and sialidosis. It sometimes is known as cherry-red spot and myoclonus syndrome, cherry-red spot myoclonus **epilepsy** syndrome, or myoclonus and cherry-red spot syndrome, in reference to characteristic symptoms of the disorder. Other names include glycoprotein neuraminidase deficiency, NEUG deficiency, NEU or NEU1 deficiency, and neuraminidase 1 deficiency. Sialidosis type I sometimes is referred to as juvenile sialidosis and type II as infantile sialidosis, in reference to the age of onset.

Lysosomal storage diseases

Lysosomes are membrane-bound spherical compartments or vesicles within the cytosol, the semi-fluid areas of cells. Lysosomes contain more than 50 different enzymes that are responsible for digesting, or hydrolyzing, large molecules and cellular components. These include proteins, polysaccharides, which are long, linear or branched chains of sugars, and lipids, which are large insoluble biomolecules that are usually built from fatty acids. The smaller breakdown products from the lysosomes are recycled to the cytosol.

Neuraminidase deficiency is one of at least 41 genetically-distinct lysosomal storage diseases. These disorders result from mutations in the genes encoding the hydrolytic enzymes of the lysosome. In these disorders, some of the macromolecules in the lysosomes cannot be degraded and they, or their partial-breakdown products, accumulate there. The lysosomes swell to the point where cellular function is disrupted.

Neuraminidase deficiency, particularly sialidosis type II, commonly has been classified as the lysosomal storage disease called **mucolipidosis** type I (ML I), formerly lipomucopolysaccharidosis. This is because the symptoms of neuraminidase deficiency are similar to various mucolipidosis disorders. However mucolipidoses are characterized by the accumulation of large and complex lipid-polysaccharides. In contrast, neuraminidase deficiency leads to the accumulation of specific types of short chains of sugar called oligosaccharides and of certain proteins with oligosaccharides attached to them, called glycoproteins. Thus, it may be more appropriate to classify neuraminidase deficiency as an oligosaccharide storage disease, since it leads to the accumulation of excess oligosaccharides in various tissues throughout the body and the excretion of oligosaccharides.

Neuraminidase

Neuraminidase, or sialidase, is a type of enzyme known as an exoglycosidase because it cleaves terminal sugar units, or residues, off oligosaccharides. Specifically, neuraminidase cleaves, or hydrolyzes, terminal sialic acid residues. Sialic acid, also known as N-acetylneuraminic acid, is a type of sugar molecule that often is at an end of an oligosaccharide. The oligosaccharides with sialic acid residues may be attached to proteins (glycoproteins). Therefore, neuraminidase deficiency prevents the proper breakdown of oligosaccharides and glycoproteins that contain sialic acid and the disorder is characterized by the accumulation and excretion of these substances.

In addition to interfering with the lysosomal breakdown of sialic acid compounds, neuraminidase deficiency can lead to abnormal proteins. Following protein synthesis, some lysosomal enzymes reach the lysosome in an inactive form and require further processing for activation. One such processing step is the neuraminidase-catalyzed removal of sialic acid residues from oligosaccharides on the enzymes. Lysosomal hydrolases that require further processing by neuraminidase include acid phosphatase, alpha-mannosidase, arylsulfatase B, and alpha-glucosidase.

Under conditions of neuraminidase deficiency, sialyloligosaccharides accumulate in various cells, including lymphocytes (white blood cells that produce antibodies), fibroblasts (connective tissue cells), bone marrow cells, Kupffer cells of the liver, and Schwann cells, which form the myelin sheaths of nerve fibers. Furthermore, proteins with sialic acid attachments accumulate and can be detected in fibroblasts and in the urine.

Neuraminidase exists in the lysosome in a high-molecular-weight complex with three other proteins: the enzyme beta-galactosidase, the enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS), and a multi-functional enzyme called protective protein/cathepsin A (PPCA). Neuraminidase must be associated with PPCA in order for the neuraminidase to reach the lysosome. Once inside the lysosome, PPCA mediates the association of as many as 24 neuraminidase molecules to form active neuraminidase. The active enzyme remains associated with PPCA and beta-galactosidase, which appear to be necessary for protecting and stabilizing the neuraminidase activity. A distinct lysosomal storage disease, neuraminidase deficiency with beta-galactosidase deficiency, or galactosialidosis, results from mutations in the gene encoding PPCA. In this disorder, both neuraminidase and beta-galactosidase are deficient.

Genetic profile

Inheritance of neuraminidase deficiency

Neuraminidase deficiency is an autosomal recessive disorder that can be caused by any one of a number of different mutations in the NEU1 gene encoding the lysosomal neuraminidase. The disorder is autosomal because the NEU1 gene is located on chromosome 6, rather than on the X or Y sex **chromosomes**. The disorder is recessive because it only develops when both genes encoding neuraminidase, one inherited from each parent, are defective; however, the two defective NEU1 genes do not need to carry the same mutations. If the two mutations are identical, the individual is a homozygote. If the two mutations are different, the affected individual is called a compound heterozygote. Individuals with one defective gene and one normal gene encoding neuraminidase may have reduced levels of the active enzyme, but they do not have symptoms of neuraminidase deficiency.

All of the offspring of two parents with neuraminidase deficiency will inherit the disorder. All of the offspring of one parent with neuraminidase deficiency and one parent with a single defective NEU1 gene will inherit at least one defective NEU1 gene. They will have a 50% chance of inheriting two defective genes and, therefore, developing neuraminidase deficiency. The offspring of one parent with neuraminidase deficiency and one parent with normal NEU1 genes will inherit a defective gene from the affected parent, but will not develop neuraminidase deficiency. The offspring of parents who both carry one defective NEU1 gene have a 50% chance of inheriting one defective NEU1 gene and a 25% chance of inheriting two genes and developing neuraminidase deficiency. Finally, the children of one parent with a single defective NEU1 gene and one parent with normal NEU1 genes will have a 50% chance of inheriting the defective gene, but will not develop neuraminidase deficiency.

Mutations in the NEU1 gene

A number of different mutations that can cause neuraminidase deficiency have been identified in the NEU1 gene. The type of neuraminidase deficiency, sialidoses types I or II, as well as the severity of the symptoms, depends on the specific mutation(s) that are present. Some mutations change one amino acid out of the 415 amino acids that compose a single neuraminidase molecule. Other identified mutations result in a shortened enzyme. Many of the identified mutations are clustered in one region on the surface of the protein. These mutations result in a sharp reduction in the activity of the enzyme and lead to the rapid degradation of neuraminidase inside the lysosome.

Some mutations in the NEU1 gene lead to a complete absence of neuraminidase activity, with little or no neuraminidase enzyme present in the lysosomes. These mutations usually result in the severe, infantile-onset, type II sialidosis. Other mutations result in an inactive protein that is present in the lysosome. These mutations generally result in juvenile-onset, type II sialidosis, with symptoms of intermediate severity. Some mutations significantly reduce, but do not obliterate, neuraminidase activity in the lysosome. Individuals with at least one mutated gene of this type are not completely neuraminidase-deficient and have mild, type I sialidosis. Occasionally, individuals have multiple mutations in the NEU1 gene, leading to more severe forms of neuraminidase deficiency.

Demographics

Neuraminidase deficiency is an extremely rare disorder. Because of its similarities to many other disorders, it has been difficult to determine its frequency. In the United States, it is estimated to occur in one out of every 250,000 live births. In Australia, the estimate is one out of 4.2 million. Since neuraminidase deficiency is an autosomal rather than a sex-linked disorder, it occurs equally in males and females.

As an autosomal recessive disorder, neuraminidase deficiency requires two copies of the defective gene, one inherited from each parent. Thus, neuraminidase deficiency is much more common in the offspring of couples who are related to each other (consanguineous marriages), such as first or second cousins.

Sialidosis type I appears to be more common among Italians. Type 2 sialidosis seems to occur more frequently among Japanese.

Signs and symptoms

The clinical symptoms of neuraminidase deficiency are similar to the symptoms of the mucolipidoses, including I-cell disease (mucolipidosis II) and pseudoHurler polydystrophy (mucolipidosis III). Furthermore, the clinical distinctions between sialidoses types I and II may not be clearly defined.

Sialidosis type I

The symptoms of sialidosis type I do not appear until the second decade of life. Infants and children with this form of neuraminidase deficiency may have a normal

appearance and grow normally until adolescence. At that time, the appearance of red spots in both eyes, known as cherry-red macules or cherry-red macular spots, may be one of the first symptoms of neuraminidase deficiency. Eventually, color and/or night blindness may develop. Cataracts may occur and vision may deteriorate gradually into blindness.

Other symptoms of sialidosis type I include myoclonus. These are sudden involuntary muscle contractions, which may eventually develop into myoclonic seizures. The myoclonus may become debilitating, even in sialidosis type I. Individuals with this form of neuraminidase deficiency may have increased deep tendon reflexes and may develop tremors and various other neurological conditions. There may be a progressive loss of muscle coordination, called ataxia, and walking and standing may become increasingly difficult. Speech problems, such as slurring, may develop.

The above symptoms also may occur in sialidosis type II. However, in addition to the age of onset, type I can be distinguished from type II by the absence of skeletal and facial abnormalities. Furthermore, individuals with this form of neuraminidase deficiency have normal intelligence.

Sialidosis type II

Sialidosis type II has three forms: congenital or neonatal, with symptoms present at or before birth; infantile, with symptoms developing at birth or during the first year of life; and juvenile, with symptoms developing between the ages of two and twenty.

Symptoms of sialidosis type II vary from mild to severe, but are always more severe than in type I sialidosis. With neonatal onset, infants may be born with ascites (accumulation of fluid in the abdominal cavity), swollen liver and spleen (hepatosplenomegaly), hernia of the umbilicus or the groin, and other abnormalities. With severe forms of the disorder, children may die in infancy. With milder forms, they may show no symptoms for the first ten years of life. Thus, ascites, hepatosplenomegaly, and hernias may develop later. Children with neuraminidase deficiency may grow abnormally fast. Cherry-red macules, myoclonus, and other neurological abnormalities, including tremors, may be present. The myoclonus may progress into a form of epilepsy. These children may have mild to severe mental retardation.

Sialidosis type II is characterized by a variety of skeletal malformations (dysostosis multiplex). Obvious symptoms may include distinctive, coarse facial features (called coarse facies), a short trunk with relatively long legs and arms, and a prominent breast bone (pectus carinatum). In addition, there may be a lack of muscle tone and strength (hypotonia) and the progressive wasting of muscular tissue.

The hearing may be affected in sialidosis type II. Individuals may have difficulty breathing (dyspnea). Cardiac problems may develop and severe congenital sialidosis type II apparently can result in severely-dilated coronary arteries. Loose bowel movements are common with this form of neuraminidase deficiency.

KEY TERMS

Dysostosis multiplex—A variety of bone and skeletal malformations.

Fibroblast—Cells that form connective tissue fibers like skin.

Glycoprotein—A protein with at least one carbohydrate group.

Heterozygote—Having two different versions of the same gene.

Homozygote—Having two identical copies of a gene or chromosome.

Lipid—Large, complex biomolecule, such as a fatty acid, that will not dissolve in water. A major constituent of membranes.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Oligosaccharide—Several monosaccharide (sugar) groups joined by glycosidic bonds.

Polysaccharide—Linear or branched macromolecule composed of numerous monosaccharide (sugar) units linked by glycosidic bonds.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

Sialic acid—N-acetylneuraminic acid, a sugar that is often at the end of an oligosaccharide on a glycoprotein.

Vacuolation—The formation of multiple vesicles, or vacuoles, within the cytosol of cells.

Diagnosis

Neuraminidase activity

Typically, neuraminidase deficiency is diagnosed by measuring the activity of the enzyme in cultures of fibroblast cells that have been grown from cells obtained via a skin biopsy. Lysosomal neuraminidase also can be measured in leukocytes (white blood cells). However, human cells have two other types of neuraminidase, encoded by different genes. One of these enzymes is present in the cell membrane and the other is in the cytosol of various cells, including leukocytes. These enzymes are not deficient in sialidosis and their activities can interfere with the measurement of lysosomal neuraminidase.

Neuraminidase activity usually is measured by testing the ability of fibroblast cell preparations to hydrolyze, or cleave, a synthetic compound such as 4-methylumbelliferyl-D-N-acetylneuraminic acid. Hydrolysis by neuraminidase liberates 4-methylumbelliferone, which is a compound with a fluorescence that can be measured accurately. Neuraminidase is an unstable enzyme and special precautions are needed to test for its activity. The normal range of neuraminidase activity in fibroblasts is 95-653 picomoles per minute per milligram of protein. In leukocytes, the normal range is 6-60 picomoles per minute per milligram of protein. Levels of active neuraminidase are much lower in sialidosis type II as compared with type I.

Urine tests

Neuraminidase deficiency may be diagnosed by screening the urine for the presence of sialyloligosaccharides, using chromatography to separate the components of the urine on the basis of size and charge. In unaffected individuals, sialyloligosaccharides are cleaved by neuraminidase and, therefore, are present in the urine in only very low amounts. With neuraminidase deficiency, urine levels of sialyloligosaccharides may be three to five times higher than normal. Sialylglycopeptides, or partially-degraded proteins with sialyloligosaccharides still attached, also can be detected in the urine under conditions of neuraminidase deficiency.

Histology

Neuraminidase deficiency and other lysosomal storage diseases interfere with the normal lysosomal breakdown of cellular components. As a result, the lysosomes may fill up with large molecules that are only partially digested. In the case of neuraminidase deficiency, the lysosomes fill up with sialyloligosaccharides and sialylglycopeptides. These swollen lysosomes may form inclusion bodies and give cells a vacuolated appearance that is diagnostic of lysosomal storage disease. Neuraminidase deficiency may be diagnosed by histological, or microscopic, examination of a number of different types of cells that may show this cytosolic vacuolation. These cells include the Kupffer cells of the liver, lymphocytes, bone marrow cells, epithelial skin cells, and fibroblasts.

Sialidosis type II

Infants with sialidosis type II often have visual symptoms of the disorder at birth, including facial and skeletal abnormalities. Skeletal x rays may be used to diagnose the dysostosis multiplex of this type of neuraminidase deficiency. Magnetic resonance imaging (MRI) may be used to determine brain atrophy.

Prenatal diagnosis

Neuraminidase deficiency may be diagnosed prenatally. In at-risk fetuses, cultured fetal cells from the amniotic fluid, obtained by **amniocentesis**, or cultured chorionic villi cells, obtained by chorionic villi sampling in the early weeks of pregnancy, may be tested for neuraminidase activity. Since carriers of a single mutated NEU1 gene do not have symptoms of neuraminidase deficiency, it may be difficult to recognize an at-risk fetus unless there is a family history of the disorder.

Treatment and management

At present, there is no treatment for neuraminidase deficiency. Rather, attempts are made to manage individual symptoms. Myoclonic seizures, in particular, are very difficult to control.

Prognosis

Individuals with sialidosis type I may have a near-normal life expectancy. However, the myoclonus may be progressively debilitating and myoclonic seizures can be fatal. Children with neonatal-onset sialidosis type II usually are stillborn or die at a young age. Those with infantile-onset sialidosis type II rarely survive through adolescence.

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ORGANIZATIONS

Canadian Society for Mucopolysaccharide and Related Diseases. PO Box 64714, Unionville, ONT L3R OM9. Canada (905) 479-8701 or (800) 667-1846. <http://www.mpssociety.ca>.

International Society for Mannosidosis and Related Diseases. 3210 Batavia Ave., Baltimore, MD 21214. (410) 254-4903. info@mannosidosis.org. <http://www.mannosidosis.org>.

National MPS Society. 102 Aspen Dr., Downingtown, PA 19335. (610) 942-0100. Fax: (610) 942-7188. info@mpssociety.org. <http://www.mpssociety.org>.

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Margaret Alic, PhD

Neuraminidase deficiency with beta-galactosidase deficiency

Definition

Neuraminidase deficiency with beta-galactosidase deficiency, commonly-known as galactosialidosis, is a rare inherited metabolic disorder with multiple symptoms that can include skeletal abnormalities, mental retardation, and progressive neurological degeneration.

Description

Neuraminidase deficiency with beta-galactosidase deficiency, or galactosialidosis, is a very rare genetic disorder with progressive signs and symptoms that are almost identical to those of neuraminidase deficiency alone, a disorder that is often called sialidosis. These symptoms can include skeletal and facial abnormalities, seizures, vision and hearing loss, cardiac and kidney problems, and mental retardation. However, as with sialidosis, the severity of the symptoms of galactosialidosis vary greatly.

Galactosialidosis is also known as Goldberg syndrome, after M. F. Goldberg and colleagues who first described the disorder in 1971. The disorder is also sometimes called protective protein/cathepsin A (or PPCA) deficiency, deficiency of lysosomal protective protein, or deficiency of cathepsin A.

Galactosialidosis is caused by a mutation, or change, in the **gene** encoding an enzyme called protective protein/cathepsin A (PPCA). PPCA forms a very large multienzyme complex with three other enzymes: beta-galactosidase, N-acetylgalactosamine-6-sulfate sulfatase (GALNS), and alpha-N-acetylneuraminidase. The latter enzyme is commonly referred to as neuraminidase or sialidase. Whereas sialidosis is caused by a mutation in the gene encoding neuraminidase, a mutation in the gene encoding PPCA can affect the activities of all of the enzymes in the complex. However neuraminidase is the enzyme that is most dependent on PPCA. Without functional PPCA, there is little or no neuraminidase activity. Although beta-galactosidase activity is reduced, a significant amount of active enzyme remains. Therefore, the symptoms of neuraminidase deficiency with beta-galactosidase deficiency are more similar to those of sialidosis than to those of beta-galactosidase deficiency. Mutations in the gene encoding beta-galactosidase can result in the disorders known as **GM1 gangliosidosis** (beta-galactosidosis) or Morquio B disease.

Galactosialidosis is subdivided into three types, depending on the age of onset: severe, neonatal or early-infantile; milder, late-infantile; and juvenile/adult. The juvenile/adult form is the most common. There also is an atypical form of galactosialidosis. The type and severity of the disorder depends on the specific mutation(s) present in the genes encoding PPCA.

Lysosomal storage diseases

Neuraminidase, beta-galactosidase, PPCA, and GALNS are all enzymes that function inside lysosomes. Lysosomes are membrane-bound spherical compartments or vesicles within the cytosol (fluid part) of cells. Lysosomes contain more than 50 different enzymes that are responsible for digesting, or hydrolyzing, large molecules and cellular components. These include proteins, polysaccharides (long, linear or branched chains of sugars), and lipids, which are large, insoluble biomolecules that are usually built from fatty acids. The smaller breakdown products from the lysosome are recycled back to the cytosol.

Galactosialidosis is one of at least 41 genetically distinct lysosomal storage diseases. In these disorders, some of the macromolecules in the lysosome cannot be degraded. Instead, these large molecules, or their partial-breakdown products, accumulate, and the lysosomes swell to the point that cellular function is disrupted.

Neuraminidase deficiency

Neuraminidase removes sialic acid from the ends of oligosaccharides, which are relatively short chains of sugars. Sialic acid, also known as N-acetylneuraminic acid, is a type of sugar molecule that often is at an end of an oligosaccharide. These oligosaccharides with terminal sialic acid residues may be attached to proteins, called glycoproteins.

Neuraminidase deficiency prevents the breakdown of oligosaccharides and glycoproteins that contain sialic acid and leads to the accumulation and excretion of these substances. It also can lead to the production of abnormal proteins. Following protein synthesis, some lysosomal enzymes reach the lysosome in an inactive form and require further processing for activation. One such processing step is the neuraminidase-catalyzed removal of sialic acid residues from oligosaccharides on enzymes. Thus, under conditions of neuraminidase deficiency, other lysosomal enzymes may not behave properly.

Protective protein/cathepsin A

PPCA is required for the transport of neuraminidase to the lysosome. Once inside the lysosome, the enzymatic activity of PPCA may be involved in the activation of neuraminidase. Furthermore, PPCA mediates the association of multiple molecules of neuraminidase and beta-galactosidase, as well as GALNS. In the absence of PPCA, all three enzymes are rapidly degraded in the lysosome. Thus, PPCA protects and stabilizes these enzyme activities. In the absence of PPCA, substrates for these enzymes may accumulate to dangerous levels.

Gangliosides are very complex components of cell membranes. They are made up of a long-chain amino alcohol called sphingosine, a long-chain fatty acid, and a very complex oligosaccharide that contains sialic acid. The lysosomal beta-galactosidase is responsible for hydrolyzing gangliosides.

GALNS catalyzes the first step in the lysosomal breakdown of a special type of sugar called keratan sulfate. Both gangliosides and keratan sulfate may accumulate in galactosialidosis.

In addition to its protective functions, PPCA has at least three enzymatic activities of its own, including the ability to cleave (break apart), or hydrolyze, other proteins. Some of the neurological abnormalities that develop with galactosialidosis may be due to the loss of this activity, particularly PPCAs ability to cleave endothelin-1. This peptide is overabundant and abnormally distributed in the neurons and glial cells of the brain and spinal cord of individuals with galactosialidosis.

Genetic profile

Galactosialidosis is an autosomal recessive disorder that can be caused by any one of a number of different mutations in the gene encoding PPCA. This gene is known as PPGB, for beta-galactosidase protective protein. The disorder is autosomal since the PPGB gene is located on chromosome 20, rather than on the X or Y sex **chromosomes**. The disorder is recessive because it only develops when both genes encoding PPCA, one inherited from each parent, are abnormal. However, the two defective genes do not need to carry the same mutations. If the two mutations are identical, the individual is a homozygote. If the two mutations are different, the affected individual is called a compound heterozygote.

PPCA mutations

The type of galactosialidosis and the severity of the symptoms depend on the specific mutations that are present. In general, the higher the level of PPCA activity in the lysosomes, the milder the characteristics of galactosialidosis, and the later the onset of disease.

With some mutations of the PPGB gene, very little of the precursor protein to PPCA is produced and there is no mature PPCA in the lysosome. With other mutations, the precursor protein may not be correctly processed into mature protein. Some individuals with severe early-infantile galactosialidosis carry mutations that prevent precursor PPCA from being targeted to the lysosome. The lysosomes of these individuals have no PPCA.

In contrast, individuals with the late-infantile form of galactosialidosis carry at least one mutant PPGB gene whose product can reach the lysosome. However, there may be only a small amount of PPCA in the lysosome; the PPCA may lack enzymatic activity; the PPCA chains may be unable to combine to form the normal two-chained form; or the PPCA may be degraded rapidly. Nevertheless, with these mutations, the symptoms of galactosialidosis are mild and progress very slowly with no mental retardation.

Other identified mutations prevent the PPCA molecules from folding properly or shorten the PPCA protein so that it cannot form a complex with the other enzymes.

Compound heterozygotes, with different mutations in their PPGB genes, usually have symptoms that are intermediate in severity between those of homozygotes for each of the two mutations. Occasionally, the symp-

toms of a compound heterozygote may be more mild than those of either homozygote, because the two mutant PPCA proteins can complement, or compensate, for each other's abnormalities.

Demographics

As an autosomal recessive disorder, neuraminidase deficiency with beta-galactosidase deficiency occurs with equal frequency among males and females. Since it requires two defective copies of the PPGB gene, one inherited from each parent, it is much more common in the offspring of couples who are related to each other (consanguineous marriages), such as first or second cousins.

Galactosialidosis appears to occur with the highest frequency among Japanese. The juvenile/adult form is particularly common among Japanese and specific mutations in the PPGB gene occur with a high frequency in this population.

Signs and symptoms

Although the features of galactosialidosis vary greatly, they are very similar to those of neuraminidase deficiency (sialidosis). These progressive symptoms include red spots in the eyes, known as cherry-red macules. Eventually, the corneas may be become cloudy and cataracts and blindness may develop. Hearing loss is also common with galactosialidosis.

Myoclonus are sudden involuntary muscle contractions, which may eventually develop into myoclonic seizures. The myoclonus may become debilitating. Tremors and various other neurological conditions may develop. There may be a progressive loss of muscle coordination, called ataxia, and walking and standing may become increasingly difficult.

Small red skin lesions called angiokeratoma are signs of galactosialidosis. Swollen liver and spleen (hepatosplenomegaly) may develop. Cardiac disease can be one of the major consequences of the disorder.

Symptoms of the more severe forms of galactosialidosis include coarse or malformed facial features and a variety of skeletal malformations (dysostosis multiplex), including short stature. Mental retardation also may be present. Galactosialidosis is one cause of nonimmune **hydrops fetalis**, the excessive accumulation of fluid in the fetus.

KEY TERMS

Dysostosis multiplex—A variety of bone and skeletal malformations.

Fibroblast—Cells that form connective tissue fibers like skin.

Galactosialidosis—The inherited disorder known as neuraminidase deficiency with beta-galactosidase deficiency.

Ganglioside—A complex membrane lipid made up of a long-chain fatty acid, a long-chain amino alcohol, and an oligosaccharide containing sialic acid.

Glycoprotein—A protein with at least one carbohydrate group.

Heterozygote—Having two different versions of the same gene.

Homozygote—Having two identical copies of a gene or chromosome.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Oligosaccharide—Several monosaccharide (sugar) groups joined by glycosidic bonds.

Polysaccharide—Linear or branched macromolecule composed of numerous monosaccharide (sugar) units linked by glycosidic bonds.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

Sialic acid—N-acetylneuraminic acid, a sugar that is often at the end of an oligosaccharide on a glycoprotein.

Sialidosis—An inherited disorder known as neuraminidase deficiency.

Vacuolation—The formation of multiple vesicles, or vacuoles, within the cytosol of cells.

Diagnosis

Early-infantile onset

Some findings of the disorder, including facial and skeletal abnormalities, may be apparent at birth. Skeletal x rays may be used to diagnose dysostosis multiplex. Magnetic resonance imaging (MRI) or computer tomography (CT) scans may be used to determine brain atrophy. An electroencephalogram (EEG) may indicate epileptic activity.

Neuraminidase activity

Typically, neuraminidase deficiency is diagnosed by measuring the activity of the enzyme in cultures of fibroblast cells (connective tissue cells) that have been grown from cells obtained by a skin biopsy. Neuraminidase activity usually is measured by testing the ability of fibroblast cell preparations to hydrolyze, or cleave, a synthetic compound such as 4-methylumbelliferyl-D-N-acetylneuraminic acid. Hydrolysis by neuraminidase liberates 4-methylumbelliferone, which is a compound with a fluorescence that can be measured accurately. The normal range of neuraminidase activity in fibroblasts is 95–653 picomoles per min per mg of protein. With galactosialidosis, neuraminidase activity in fibroblasts may be less than 4% of normal.

Beta-galactosidase activity

Beta-galactosidase activity in blood cells is measured in much the same way as neuraminidase activity in fibroblasts. Using the substrate 4-methylumbelliferyl-alpha-D-galactopyranoside, the fluorescence of 4-methylumbelliferone that is liberated through the action of beta-galactosidase is measured.

In severe forms of galactosialidosis, beta-galactosidase activity is less than 15% of normal and neuraminidase activity is less than 1% of normal. The combination of low beta-galactosidase and low neuraminidase in fibroblasts, with normal levels of other lysosomal enzymes, is diagnostic for galactosialidosis.

PPCA activity

The enzymatic activity of PPCA also can be measured in fibroblasts. In the early-infantile form of galactosialidosis, PPCA activity may be completely lacking. A small amount of PPCA activity (2–5% of normal) usually is present in the lysosomes of individuals with other forms of galactosialidosis. The highest levels of PPCA activity are associated with the least severe and later-onset forms of the disorder. Carriers with a single mutated PPGB gene may have only half of the normal level of PPCA activity, although they are without symptoms of the disorder.

Histology

In neuraminidase deficiency with beta-galactosidase deficiency, the lysosomes fill with sialyloligosaccharides and sialylglycopeptides (partially degraded proteins with sialyloligosaccharides still attached). These swollen lysosomes may form inclusion bodies and give cells a vacuolated appearance that is diagnostic of lysosomal storage disease.

Neuraminidase deficiency may be diagnosed by histological, or microscopic, examination of a number of different types of cells that may show this cytosolic vacuolation. These cells include the Kupffer cells of the liver, lymphocytes (white blood cells that produce antibodies), bone marrow cells, epithelial skin cells, fibroblasts, and Schwann cells, which form the myelin sheaths of nerve fibers.

Urine tests

Neuraminidase deficiency may be diagnosed by screening the urine for the presence of sialyloligosaccharides, using chromatography to separate the components of the urine on the basis of size and charge. In unaffected individuals, sialyloligosaccharides are cleaved by neuraminidase and, therefore, are present in the urine in only very low amounts. With neuraminidase deficiency, urine levels of sialyloligosaccharides may be three to five times higher than normal.

Sialylglycopeptides can be detected in the urine under conditions of neuraminidase deficiency. In neuraminidase deficiency with beta-galactosidase deficiency, keratan sulfate, which accumulates because of the low activity of GALNS, also can be identified in the urine.

Prenatal diagnosis

Galactosialidosis may be diagnosed prenatally. In at-risk fetuses, cultured fetal cells from the amniotic fluid (amniocytes), obtained by **amniocentesis**, or cultured chorionic villi cells, obtained by chorionic villi sampling (CVS) in the early weeks of pregnancy, may be tested for neuraminidase and beta-galactosidase activities. Furthermore, the enzymatic activities of PPCA can be measured in amniocytes and chorionic villi. PPCA activity is normally very high in these cells and low activity is an indication of an affected fetus. However, since carriers of a single mutated PPGB gene do not have symptoms of galactosialidosis, it may be difficult to recognize an at-risk fetus unless there is a family history of the disorder.

Treatment and management

At present, there is no treatment for neuraminidase deficiency with beta-galactosidase deficiency. Rather, attempts are made to manage individual symptoms. Myoclonic seizures, in particular, are very difficult to control. Bone marrow transplantation is being studied as a treatment for severe galactosialidosis.

Prognosis

The prognosis for individuals with this disorder varies greatly depending on the specific genetic mutation,

which determines the age of onset and severity of the disease. Individuals with mild forms of galactosialidosis may have nearly normal life expectancies. However, the early-infantile form of galactosialidosis usually results in death shortly after birth.

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Margaret Alic, PhD

Neurofibromatosis

Definition

Neurofibromatosis (NF), or von Recklinghausen disease, is a disorder which causes development of multiple soft tumors (neurofibromas). These tumors occur under the skin and throughout the nervous system (cells which control body movement and sensation).

Description

Neural crest cells are primitive cells which exist during fetal development. These cells eventually turn into cells that form nerves throughout the brain, spinal cord, and body. Collectively, this system of nerve cells is called the nervous system, which coordinates movement and sensation. Some nerve cells carry impulses from the brain to muscles or other peripheral structures, hence the name peripheral nervous system. Another group of nerve cells called the central nervous system are capable of transmitting sensation back to the brain for interpretation (such as feeling cold or hot).

In neurofibromatosis, a genetic defect causes these neural crest cells to develop abnormally. This results in numerous tumors and malformations of the nerves, bones, and skin.

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

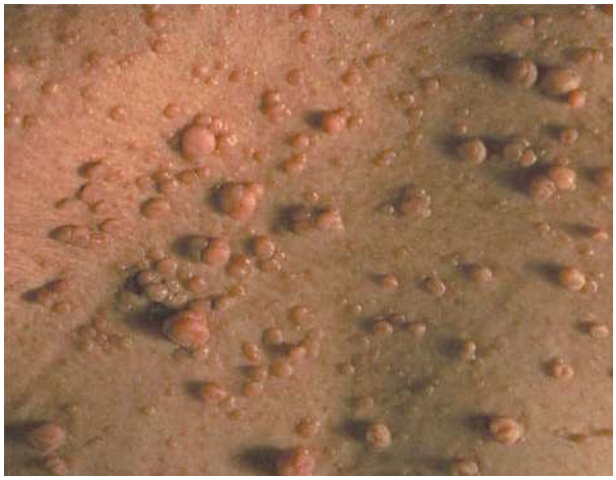
Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Neurofibroma—A soft tumor usually located on a nerve.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

Genetic profile

Both forms of neurofibromatosis are caused by a defective **gene**. NF-1 is due to a defect on chromosome 17; NF-2 results from a defect on chromosome 22. Both of these disorders are inherited as a dominant trait. This means that anybody who receives just one defective gene will have the disease. However, a family pattern of NF is only evident for about half of all cases of NF. The other cases of NF occur due to a spontaneous mutation (a spontaneous and permanent change in the structure of a specific gene). Once a spontaneous mutation has been established in an individual it is then possible to be passed on to any offspring. The chance of a person with NF passing on the NF gene to their child is 50%. There are different pathologic alleles (variations of the mutant gene). The frequency of spontaneous (new) mutations is very high and causes for this are still unknown.



The large and small protrudings growths on the back of this patient are characteristic of neurofibromatosis. *(Custom Medical Stock Photo, Inc.)*

Demographics

Neurofibromatosis-I occurs in about one of every 4,000 births. Neurofibromatosis-I is one of the most common **genetic disorders** that is dominantly inherited. Two types of NF exist, NF-1 (90% of all cases), and NF-2 (10% of all cases).

Signs and symptoms

NF-1 has a number of possible signs and can be diagnosed if any two of the following are present:

- The presence of café-au-lait (French for coffee-with-milk) spots. These are patches of tan or light brown skin, usually about five to 15 mm in diameter. Nearly all patients with NF-1 will display these spots.
- Multiple freckles in the armpit or groin area.
- Ninty percent of patients with NF-1 have tiny tumors called Lisch nodules in the iris (colored area) of the eye.
- Neurofibromas. These soft tumors are the hallmark of NF-1. They occur under the skin, often located along nerves or within the gastrointestinal tract. Neurofibromas are small and rubbery, and the skin overlying them may be somewhat purple in color.
- Skeletal deformities, such as a twisted spine (**scoliosis**), curved spine (humpback), or bowed legs.
- Tumors along the optic nerve (the nerve cells which transmit a visual stimulus to the back part of the brain called the occipital lobe, for intrepretation), which cause vision disturbance occurs in about 20% of patients.
- The presence of NF-1 in a patient's parent, child, or sibling.
- Hypertension, or elevated blood pressure.

There are very high rates of speech impairment, learning disabilities, and attention deficit disorder in children with NF-1. Other complications include the development of a seizure disorder (an abnormal firing of nerve cells in muscles, causing severe contractions, sometimes involving the whole body), or abnormal accumulation of fluid within the brain (a condition called **hydrocephalus**). A number of cancers are more common in patients with NF-1. These include a variety of types of malignant brain tumors, as well as leukemia, and cancerous tumors of certain muscles (rhabdomyosarcoma), the adrenal glands (pheochromocytoma), or the kidneys (Wilms' tumor).

Patients with NF-2 do not necessarily have the same characteristic skin symptoms (café-au-lait spots, freckling, and neurofibromas of the skin) that appear in NF-1. The characteristic symptoms of NF-2 are due to tumors along the acoustic nerve. Interfering with the function of this nerve results in the loss of hearing; and the tumor may spread to neighboring nervous system structures, causing weakness of the muscles of the face, headache, dizziness, poor balance, and uncoordinated walking. Cloudy areas on the lens of the eye (called cataracts) frequently develop at an unusually early age. As in NF-1, the chance of brain tumors developing is unusually high.

Diagnosis

Diagnosis is based on the broad spectrum of clinical signs previously described, which usually can be detected by careful physical examination, ophthalmologic evaluation (visualizing the structures in the eye) and audiogram (test to measure hearing ability). Diagnosis of NF-1 requires that at least two of the listed signs are present. Diagnosis of NF-2 requires the presence of either a mass on the acoustic nerve or another distinctive nervous system tumor. An important diagnostic clue for either NF-1 or NF-2 is the presence of the disorder in a patient's parent, child, or sibling. A test to detect a protein (the end-products of a gene) relevant to NF-1 mutagenesis has been created, but accuracy for this procedure has not been established.

Monitoring the progression of neurofibromatosis involves careful testing of vision and hearing. X ray studies of the bones are frequently indicated to detect for the development of deformities. CT scans and MRI scans are performed to track the development/progression of tumors in the brain and along the nerves. Auditory evoked potentials (the electric response evoked in the cerebral cortex by stimulation of the acoustic nerve) may be helpful to determine acoustic nerve involvement, and EEG (electroencephalogram, a record of electrical

impulses in the brain) may be required for patients with suspected seizures. Regular blood pressure monitoring is also advised.

Treatment

There are no available treatments for the disorders which underlie either type of neurofibromatosis. To some extent, the symptoms of NF-1 and NF-2 can be treated individually. Skin tumors can be surgically removed. Some brain tumors, and tumors along the nerves, can be surgically removed, or treated with drugs (chemotherapy) or x-ray treatments (radiation therapy). Twisting or curving of the spine and bowed legs may require surgical treatment, or the wearing of a special brace.

Prognosis

Prognosis varies depending on the tumor type which develops. As tumors grow, they begin to destroy surrounding nerves and structures. Ultimately, this destruction can result in blindness, deafness, increasingly poor balance, and increasing difficulty with the coordination necessary for walking. Deformities of the bones and spine can also interfere with walking and movement. When cancers develop, prognosis worsens according to the specific type of **cancer**.

Prevention

There is no known way to prevent the approximately 50% of all NF cases that occur due to a spontaneous change in the genes (mutation). New cases of inherited NF can be prevented with careful **genetic counseling**. A person with NF can be made to understand that each of his or her offspring has a 50% chance of also having NF when a parent has NF. Special tests can be performed on the fetus (developing baby) during pregnancy to determine if the fetus will be born with this disorder. **Amniocentesis** (where a needle is passed through the mother's abdomen into the amniotic sac which contains the amniotic fluid and cushions the developing fetus) or chorionic villus sampling (a procedure involving extraction of a tissue sample from the placenta, the structure which connects the fetal blood with the mother, necessary for nutrient and waste exchange) are two techniques which allow small amounts of fetal **DNA** (deoxyribonucleic acid, the chemical which contains specific codes which determine genetic makeup of an individual) removed for analysis. The tissue can then be examined for the presence of the parent's genetic defect. Some families choose to use this information in order to prepare for the arrival of a child with a serious medical condition. Other families may choose not to continue the pregnancy.

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The National Neurofibromatosis Foundation, Inc. 95 Pine St., 16th Floor, New York, NY 10005. (800)323-7938. <http://nf.org>.

Neurofibromatosis, Inc. 8855 Annapolis Rd., #110, Lanham, MD 20706-2924. (800) 942-6825.

Laith Farid Gulli, MD

Niemann-Pick disease

Definition

Niemann-Pick disease (NPD) is a disorder of fat metabolism that causes abnormalities of the skin, eyes, musculoskeletal system, nervous system, liver, and lymphoid organs. It is named for German pediatricians Albert Niemann (1880-1921) and Ludwig Pick (1898-1935). Six types of the disease have been identified (A, B, C, D, E, and F).

Description

Niemann-Pick disease is inherited through an autosomal recessive trait. The different types of NPD are characterized by an abnormal accumulation of sphingomyelin. A sphingomyelin is any group of sphingolipids (consists of a lipid and a sphingosine) containing phosphorus. It occurs primarily in the tissue of the nervous system.

KEY TERMS

Hepatosplenomegaly—Enlargement of the liver and spleen.

Macula—Abnormal pigmentation in the tissue of the eye.

Sphingomyelin—A group of sphingolipids containing phosphorus.

Sphingomyelinase—Enzyme required to breakdown sphingomyelin into ceramide.

Some characteristics of Niemann-Pick disease may be common for all types. Common symptoms include jaundice, hepatosplenomegaly (enlargement of the liver and spleen), physical and mental impairment, and feeding difficulties. Symptoms for most types of NPD (A, B, C, and D) are seen in infancy or early childhood.

Alternate names associated with the NPD disorder are lipid histiocytosis, sphingomyelin lipidosis, and sphingomyelinase deficiency.

Genetic profile

Niemann-Pick disease is caused by an autosomal recessive genetic trait, therefore the condition will not appear unless a person receives the same defective **gene** for fat metabolism from each parent. This means that if a person is heterozygous for the trait then they will be a carrier and if they are homozygous then they will show the trait. There is a 25% chance for each pregnancy that the disorder will passed onto the child (ren) if both parents are heterozygous for the trait and a 100% chance if both parents are homozygous for the trait.

The gene for Niemann-Pick disease types A and B has been located on the short arm (p) of chromosome 11. The gene for types C and D has been located on chromosome 18. NPD types C and D are believed to be allelic disorders. This term means that the two types are due to different mutations (a change in building block sequences) of the same gene. Type E is similar to type C and may be a variant form. It is possible that type F is a mild form of type B but as of 2000 there is no supportive research.

Demographics

Niemann-Pick disease affects males and females equally and has been identified in all races. Type A is the most common form of the disease and is responsible for about 80% of NPD cases.

Types A and B occur mainly in families of eastern European Jewish descent (Ashkenazi). It is estimated that one in 75 may be carriers. Type B is also common in individuals from Tunisia, Morocco, and Algeria. Type C is more common in Spanish-Americans in southern New Mexico and Colorado. As of 2000, it is believed that over 300 people in the United States are affected with type C and an estimated one million worldwide. Type D occurs in French-Canadian descendents from Nova Scotia. Type F has been found to affect people of Spanish descent. As of 2000, it is not clear as to which populations are affected by type E.

Signs and symptoms

Type A

This is the infantile or acute form of Niemann-Pick disease. Abnormal accumulation of sphingomyelin is seen in the developing fetus. Sphingomyelin accumulation could represent 2-5% of the total body weight in individuals with type A. Symptoms may progress rapidly and include the following:

- Hepatosplenomegaly. Enlargement of the liver and spleen is due to the low levels of the enzyme sphingomyelinase. This enzyme is required to breakdown sphingomyelin in the body. The decreased levels of this enzyme cause sphingomyelin content of the liver and spleen to be abnormally high. This occurs between the ages of six and 12 months. Accurance of liver enlargement is seen more commonly than that of the spleen.
- Musculoskeletal abnormalities. Degenerative muscle weakness and floppiness may occur due to a decline in motor and intellectual functioning. This is caused by increased accumulation of sphingomyelin in the nervous system. Seizures and muscular spasms may also occur.
- Macula. Pigmentation in the tissue of the eyes may occur. Formation of cherry-red spots may be seen in approximately 50% of patients diagnosed with NPD type A. This is not visible and can only be detected using special instrumentation.
- Additional abnormalities. These include jaundice, fever, and gastrointestinal (GI) problems such as vomiting, diarrhea, and abdominal distention.

Type B

This is the chronic form of Niemann-Pick disease. Symptoms progress slowly and begin during infancy or early childhood. Like type A, type B occurs due to a deficiency of the enzyme sphingomyelinase. Neurological involvement is minimal and usually absent. Symptoms are as follows:

- Hepatosplenomegaly. Abnormal enlargement of the liver and spleen occur due to the accumulation of sphingomyelin.
- Macula. The formation of cherry-red spots on the eyes may be seen in some affected individuals.
- Additional abnormalities. These include a slow growth rate and increased incidence of respiratory infections.

Type C

This type of Niemann-Pick disease occurs due to the inability to breakdown cholesterol. This may lead to a secondary deficiency of acid sphingomyelinase. Studies have shown that there may be two types of NPD type C, NPC1 and NPC2. NPC2 is believed to be caused by a deficiency of HE1 (human epididymis-1), which is a cholesterol-binding protein. NPD type C can occur at anytime between infancy and adulthood but is usually seen in children between the ages of three and 10. The progression of symptoms in NPD type C is slow and the loss of mental and motor function usually occur in early adulthood. Symptoms are as follows:

- Hepatosplenomegaly. The liver and spleen may be moderately enlarged due to the inability to breakdown cholesterol.
- Musculoskeletal. Psychomotor dysfunction, seizures, tremors, and spasticity of the muscles result due to excessive accumulation of cholesterol in the brain. An individual with NPD type C may also exhibit extreme muscle weakness due to emotional excitement and ataxia. Ataxia is the inability to coordinate voluntary muscle movements.
- Eyes. Type C is characterized by vertical gaze palsy. This results in the difficulty or loss of up and down movement. Some individuals may experience opththalmoplegia (loss of muscle ability to move eyes). This is an impaired function of the muscles of the eyes and may cause the eyes to become stuck or fixed in an upward position.
- Additional abnormalities. These include dysarthria and jaundice. Dysarthria is the inability to form and speak words clearly. Jaundice is a yellow discoloration of the skin, eyes, and possibly the mucous membranes.

Type D

This is the Nova Scotia variant of Niemann-Pick disease. Like NPD type C, individuals with type D are unable to metabolize cholesterol properly. Individuals with type D do not suffer from a deficiency of acid sphingomyelinase. The symptoms of type D are very similar to type C but vary from case to case.

Type E

As of 2000, many researchers consider this to be a variant form of type C. NPD type E does not usually begin until adulthood and neurological impairment is rare. Symptoms include the following:

- Hepatosplenomegaly. Enlargement of the liver and spleen may occur due to the accumulation of cholesterol.
- **Dementia**. This is characterized by confusion, disorientation, deterioration of intellectual capacity and function, and impairment of the memory. Dementia is progressive and irreversible.
- Ataxia. Individuals may have an inability to coordinate voluntary muscle movements.
- Opththalmoplegia. Individuals with type E may have an inability to control the muscle movement of the eyes. This may cause the eyes to become stuck in a certain position.

Type F

This type of Niemann-Pick disease is characterized by a finding of sea-colored blue cells in the blood and/or bone marrow of individuals and therefore may be called Sea-Blue histocyte disease. It affects people of Spanish descent and may be a mild form of type B. Symptoms may include:

- Hepatosplenomegaly. Abnormal enlargement of the liver and spleen may occur in individuals with NPD type F.
- Cirrhosis. The lobes of the liver may become covered with fibrous tissue (thickened tissue). This fibrous tissue obstructs blood flow through the liver.
- Mild thrombocytopenia. Individuals with NPD type F may suffer from a decrease in the number of platelets found in the blood. Platelets are necessary for coagulation of the blood.
- Macula. Pigmentation in the tissue of the eyes may occur. Individuals may develop a white ring around the maculae of the eyes.
- Hair. Individuals may have an absence of hair in the axillary (armpit) area of the body.

Diagnosis

As of 2000, there is no objective diagnostic test for Niemann-Pick disease types D, E, and F. Types A and B are diagnosed through DNA testing or by a blood test. Blood tests for individuals with types A and B will show low levels of the enzyme sphingomyelinase in white blood cells and elevated sphingomyelin and free cholesterol.

Type C can be diagnosed by prenatal testing of fibroclastic cells to determine their ability to process and store cholesterol. This is done by testing the amniotic fluid (liquid which bathes and cushions the fetus). Formation of foam cells occurs in all types of NPD and can be determined through a biopsy of bone marrow tissue. Diagnosis of all types is made possible by taking a detailed family history and a thorough examination of the individual.

Symptoms of Niemann-Pick disease may be similar to those of Refsum syndrome (disorder of fat metabolism associated with abnormal accumulation of phytanic acid in the blood and other body tissues), **Tay-Sachs disease** (disorder found in Eastern European Jewish descendents that results in deterioration of the central nervous system), Sandhoff disease (lipid storage disorder due to a deficiency of the enzyme hexosaminidase), Gaucher's disease (lipid storage disease), and Sialidosis (metabolic disorder due to a deficiency of the enzyme alpha-neuraminidase).

Treatment and management

As of 2000, there is no specific treatment available for any type of Niemann-Pick disease. Individuals are treated on a symptomatic basis. As of 2000, individuals with NPD types A and B have not benefited from enzyme replacement therapies or organ transplants. Cholesterol lowering drugs and low cholesterol diets are often used for individuals with NPD types C and D. As of 2000, these have not been effective in slowing the progress of types C and D.

Investigational therapies are being tested for types A, B, C, and D. The possibility of treatment by bone marrow transplantation is being tested for types A and B. Studies have also been completed on the use of stem cell (a cell which produces usable tissues) transplantation as treatment for types A and B. Researchers at the National Institutes of Health are studying combinations of cholesterol lowering drugs for treatment of NPD types C and D.

Social and lifestyle issues

Individuals diagnosed with Niemann-Pick disease may want to seek counseling or attend support groups that focus on the psychological, physical, and social issues that may result due to the illness.

Parents may want to seek counseling or attend support groups that focus on the lifestyle changes associated with having a child diagnosed with Niemann-Pick disease.

Prognosis

The prognosis for all types of Niemann-Pick disease varies. In type A, death usually results in early childhood. In individuals with types C and D, death usually results in adolescence or early adulthood. Individuals with type B have a prolonged survival due to the decrease of neurological involvement. As of 2000 the prognosis for types E and F has not been adequately researched.

Affected individuals and their families may want to seek **genetic counseling**. Pregnant women can receive prenatal testing for NPD type C. Pregnant women that are carriers and have a partner that is a carrier should receive genetic counseling regarding the 25 percent chance of the child having Niemann-Pick disease.

Early diagnosis is important. Due to advances in medicine an early diagnosis may increase life expectancy.

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Laith F. Gulli, MD
Tanya Bivins, BS

Niikawa-Kuroki syndrome *see* **Kabuki syndrome**

Nijmegen breakage syndrome

Definition

Nijmegen breakage syndrome (NBS) is a condition in which **chromosomes** are susceptible to breakage and symptoms include short stature, small head size, and increased risk for learning disabilities/mental retardation, infections, and **cancer**.

Description

Nijmegen breakage syndrome gets its name from the fact that the first patient was described in Nijmegen in the Netherlands. A registry of patients is maintained there, and patients with the syndrome are susceptible to having their chromosomes break. These breaks result in rearrangements of chromosomes called translocations, in which two chromosomes exchange pieces, and inversions, in which a section of a chromosome breaks off and

rejoins the chromosome upside down. Chromosome rearrangements in NBS most commonly involve chrmosomes 7 and 14. Genes involved in the immune system, which fights infection, are located on these chromosomes; as a result of disruptions of these genes, most patients with NBS have an increased rate of infections, particularly those involving the respiratory system and the urinary tract. The chromosome breaks also increase susceptibility to cancer. People with NBS are more prone to chromosome breaks when exposed to radiation as well. Other defining features of NBS are short stature and small head size.

KEY TERMS

Balanced chromosome translocation—A rearrangement of the chromosomes in which two chromosomes have broken and exchanged pieces without the loss of genetic material.

Chromosome inversion—Rearrangement of a chromosome in which a section of a chromosome breaks off and rejoins the chromosome upside down.

Microcephaly—An abnormally small head.

Genetic profile

NBS is an autosomal recessive disease, which means that one abnormal **gene** from each parent must be inherited to develop symptoms. A person with only one defective gene copy is called a carrier and will not show signs of NBS but has a 50% chance of passing along the gene to offspring with each pregnancy. Couples in which both parents are carriers of NBS have a 25% chance in each pregnancy of conceiving an affected child. The gene for NBS is on chromosome 8 and is called the NBS1 gene, coding for a protein called nibrin, which is found in all cells throughout the body. Normal nibrin is believed to be important in the repair of **DNA** which has been damaged by breaks in both strands.

Most patients have a specific change in both copies of the nibrin gene in which a string of five DNA bases, ACAAA, is missing from a specific area of the gene, leading to a shortened, or truncated, version of nibrin. A few other mutations have been reported in single patients. All of these mutations also result in a shortened, nonfunctional version of nibrin.

Demographics

NBS is extremely rare. Approximately 70 patients have been reported. A total of 55 patients from 44 families had been reportedly enrolled in the Nijmegen registry as of 2001. Most patients have been of Slavic or other European descent, with a few patients reported from New Zealand, Mexico, and the United States.

Signs and symptoms

Virtually all patients with NBS have microcephaly, or a small head size (in the lower 3%), with about 75% having this feature present at birth. Young children with NBS show impaired growth. Babies with NBS are either born small or begin to experience growth delay during their first two years. The growth rate is normal after that, but the children always remain small for their ages. According to data available in 2001, approximately 40% have normal intelligence, 50% have borderline to mild mental retardation (IQ of 55 to 70), and 10% have moderate mental retardation (IQ of 40 to 54). As of 2001, the 55 patients studied in detail showed no correlation between head circumference at birth and IQ. There is a characteristic facial appearance, which includes a receding forehead, long nose, receding chin, extra folds of skin underneath the eyes, freckles on the nose and cheeks, large ears, and thin hair. Patients frequently have café au lait spots (areas of skin that are the color of coffee with milk), and other pigment changes in the skin and eyes.

The incidence of certain birth defects is increased in NBS, with about half of patients having malformed fingers or extra skin between the fingers (called syndactyly). A few patients have been reported to have anal malformations, lack of development of the ovaries and consequent infertility, hip abnormalities, and bone, kidney, and brain abnormalities. Notably lacking is the ataxia, which is progressive loss of coordination, seen in a disorder called ataxia-telangiectasia (A-T), which is otherwise very similar to NBS but is caused by a mutation in a different gene.

People with NBS are at increased risk for infections, most commonly affecting the respiratory tract and urinary tract. Infections of the gastrointestinal tract have also been reported. They are also at increased risk for cancer, mostly B cell lymphoma. Leukemia and other cancers have also been reported.

Diagnosis

A diagnosis of NBS is suspected in children with small head size, slow growth at birth, characteristic facial features including a receding chin and prominent nose, recurrent infections, cancer (particularly B cell lymphoma), and borderline to moderate mental retardation. Prior to the discovery of the nibrin gene, diagnosis could only be confirmed by studying the levels of immune sys-

tem proteins called immunoglobulins, looking for particular chromosomal changes involving chromosomes 7 and 14, and assessing radiation sensitivity in cells from patients.

Since the gene for NBS was discovered in 1998, it is now possible to look for a mutation in a patient's nibrin gene. As of 2001, all patients of Slavic origin and approximately 70% of the small number of patients in North America have had two copies of the common five DNA base mutation in the nibrin gene. Other North American patients have had at least one copy of another mutation unique to their family. If a mutation other than the common one is found, it is important to do further investigation to determine whether or not it causes disease, as non-disease causing changes have been reported in the nibrin gene.

Adults who are at risk for having children with NBS, such as siblings of patients, can have carrier testing to determine if they have one altered nibrin gene and are carriers for NBS. During pregnancy, the DNA of a fetus can be tested using cells obtained using the procedures called chorionic villi sampling (CVS), in which cells from the placenta are studied, or **amniocentesis**, in which skin cells from the amniotic fluid surrounding the baby are tested.

Treatment and management

As of 2001, there is no specific treatment for NBS, although folic acid (a vitamin B derivative) is recommended for prevention of chromosome breaks, since repair of these breaks is compromised in NBS. Similarly, vitamin E is recommended for prevention of further cell damage. For treatment of cancer, high doses of radiation must be avoided, since the damage inflicted on the cells could be fatal.

Prognosis

Patients with NBS have a decreased life span because of the tendency toward infection and cancer. Of the 55 patients in the NBS registry described in 2000, five had died from infections between infancy and eight years of age. Fourteen had died of cancer between the ages of two and 21 years of age. The remaining 36 living patients were between the ages of four and 30.

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Toni I. Pollin, MS, CGC

Noack syndrome *see* **Pfeiffer syndrome**

Non-polyposis colon cancer *see* **Muir-Torre syndrome**

Noonan syndrome

Definition

Noonan syndrome is a condition usually involving a heart problem found at birth, short stature, a broad or webbed neck, pectus excavatum and pectus carinatum (chest deformities), as well as a range of developmental delays. Occasionally, café-au-lait spots (a skin finding) and other features of **neurofibromatosis** may be present.

Description

First described by the pediatrician and heart specialist Jacqueline Noonan in 1963, Noonan syndrome includes numerous specific features. However, no two affected individuals typically have the exact same combination of these characteristics. As of 2001, there still is no defined list of criteria to diagnose the condition, and no molecular **genetic testing** exists to confirm a diagnosis. Therefore, attributing an individual's features to Noonan syndrome is based upon a careful review of medical and family history, a detailed physical examination, and study of other possible diagnoses.

There are three major groups of Noonan syndrome. The classical type is Noonan syndrome, Type 1 (NS1). This is also known as Noonan syndrome, Male Turner syndrome, Female pseudo-Turner syndrome, Turner phenotype with normal **karyotype**, and Pterygium colli syn-

drome. NS1 has been called Male Turner syndrome because so many features overlap between NS1 and Turner syndrome. The striking difference between the two conditions is that Turner syndrome is caused by a chromosome abnormality, and affects females only. In contrast, men and women are affected with Noonan syndrome equally.

Individuals with NS1 may often have a heart defect, pulmonic stenosis, found at birth. A chest wall abnormality is common, typically with pectus carinatum at the upper portion (near the neck) and pectus excavatum below it, creating a "shield-like" appearance. Developmental delays are sometimes a part of the condition.

Facial features such as a tall forehead, wide-set eyes, low-set ears, and a short neck are common. Young children with NS1 often have very obvious facial features, and may have a "dull" facial expression, similar to conditions caused by muscle weakness. However, facial features may change over time, and adults with Noonan syndrome often have more subtle facial characteristics. This makes the face a less obvious clue of the condition in older individuals. Other associated features in NS1 are smaller genitalia in males, as well as cryptorchidism. Some individuals with the condition develop thrombocytopenia, or a low number of blood platelets, as well as other problems with normal blood coagulation (clotting).

Another type of the condition is Noonan syndrome, Type 2 (NS2). This involves the same characteristic features as Type 1, but the **inheritance** pattern is proposed as recessive, rather than the more commonly seen dominant pattern.

The final type of the syndrome is neurofibromatosis-Noonan syndrome, also known as Noonan-neurofibromatosis syndrome, and neurofibromatosis with Noonan Phenotype. In this, individuals often have some features of both neurofibromatosis and NS1. It has been proposed that this may simply be a chance occurrence of two conditions. This is because these conditions have two distinct **gene** locations, with no apparent overlap.

Genetic profile

In 1994, Ineke van der Burgt and others discovered the gene for Noonan syndrome located on chromosome 12, on the q (large) arm. They found this through careful studies of a large Dutch family, as well as 20 other smaller families, all with people affected by Noonan syndrome. As of 2001, research studies are taking place to further narrow down the gene location. It is proposed to be at 12q24 (band 24 on the q arm of chromosome 12).

Historically, NS1 has been inherited in an autosomal dominant manner, and this is still the most common inheritance pattern for the condition. This means that an affected individual has one copy of the mutated gene, and has a 50% chance to pass it on to each of his or her children, regardless of that child's gender. As of 2000, about half of people with Noonan syndrome have a family history of it. For the other half, the mutated gene presumably occurred as a new event in their conception, so they would likely be the first person in their family to be diagnosed with the condition.

New studies have identified evidence for other inheritance patterns. van der Burgt and Brunner studied four Dutch individuals with Noonan syndrome and their families and proposed an autosomal recessive form of the condition, NS2. In autosomal recessive conditions individuals may be carriers, meaning that they carry a copy of a mutated gene. However, carriers often do not have symptoms of the condition. Someone affected with an autosomal recessive condition has two copies of a mutated gene, having inherited one copy from their mother, and the other from their father. Thus, only two carrier parents can have an affected child. For each pregnancy that two carriers have together, there is a 25% chance for them to have an affected child, regardless of the child's gender. Consanguineous parents (those that are blood-related to each other) are more likely (when compared to unrelated parents) to have similar genes. Therefore, two consanguineous parents may have the same abnormal genes, which together may result in a child with a recessive condition. The hallmark feature of the families in the Dutch study is that the parents of the affected children were consanguineous, making an autosomal recessive form of Noonan syndrome a possibility.

Demographics

As of 2001, Noonan syndrome is thought to occur between one in 1,000 to one in 2,500 live births. There appears to be no ethnic bias in Noonan syndrome, though many studies have arisen from Holland, Canada, and the United States.

Signs and symptoms

Occasionally, feeding problems may occur in infants with Noonan syndrome, because of a poor sucking reflex. Short stature by adulthood is common, though birth length is typically normal. Developmental delays may become apparent because individuals are slower to attain milestones, such as sitting and walking. Behavioral problems may be more common, but often are not significant enough for medical attention. Heart defects are common, with pulmonary stenosis being the most common defect. Muscle weakness is sometimes present, as is increased

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Café-au-lait spots—Birthmarks that may appear anywhere on the skin; named after the French coffee drink because of the light-brown color of the marks.

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Cystic hygroma—An accumulation of fluid behind the fetal neck, often caused by improper drainage of the lymphatic system *in utero*.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Neurofibromatosis—Progressive genetic condition often including multiple café-au-lait spots, multiple raised nodules on the skin known as neurofibromas, developmental delays, slightly larger head sizes, and freckling of the armpits, groin area, and iris.

Nystagmus—Involuntary, rhythmic movement of the eye.

Pectus carinatum—An abnormality of the chest in which the sternum (breastbone) is pushed outward. It is sometimes called "pigeon breast."

Pectus excavatum—An abnormality of the chest in which the sternum (breastbone) sinks inward; sometimes called "funnel chest."

Phenotype—The physical expression of an individuals genes.

Pterygium colli—Webbing or broadening of the neck, usually found at birth, and usually on both sides of the neck.

Pulmonary stenosis—Narrowing of the pulmonary valve of the heart, between the right ventricle and the pulmonary artery, limiting the amount of blood going to the lungs.

Strabismus—An improper muscle balance of the ocular musles resulting in crossed or divergent eyes.

Suture—"Seam" that joins two surfaces together.

Turner syndrome—Chromosome abnormality characterized by short stature and ovarian failure, caused by an absent X chromosome. Occurs only in females.

flexibility of the joints. Less common neurologic complications may include schwannomas, or growths (common in neurofibromatosis) of the spinal cord and brain. These schwannomas may also occur in the muscle.

Many facial features are found in Noonan syndrome, often involving the eyes. Eyes may be wide-set, may appear half-closed because of droopy eyelids, and the corners may turn downward. Some other findings, such as nystagmus and strabismus may occur. Interestingly, most people with Noonan syndrome have beautiful pale blue- or green-colored eyes. Often, the ears are low-set (lower than eye-level), and the top portion of cartilage on the ear is folded down more than usual. Hearing loss may occur, most often due to frequent ear infections. A very high and broad forehead is very common. An individual's face may take on an inverted triangular shape. As mentioned earlier, facial features may change over time. An infant may appear more striking than an adult does, as the features may gradually become less obvious. Sometimes, studying childhood photographs of an individual's presumably "unaffected" parents may reveal clues. Parents may have more obvious features of the condition in their childhood photographs.

As of 2001, chest wall abnormalities such as a shield chest, pectus carinatum, and pectus excavatum occur in 90-95% of people with NS1. These are thought to occur because of early closure of the sutures underneath these areas. Additionally, widely-spaced nipples are not uncommon. **Scoliosis** (curving of the spine) may occur, along with other spine abnormalities.

Lymphatic abnormalities may be common, often due to abnormal drainage or blockage in the lymph glands. This may cause lymphedema, or swelling, in the limbs. Lymphedema may occur behind the neck (often prenatally) and this is thought to be the cause of the broad/webbed neck in the condition. Prenatal lymphedema is thought to obstruct the proper formation of the ears, eyes, and nipples as well, causing the mentioned abnormalities in all three.

Individuals with Noonan syndrome may have problems with coagulation, shown by abnormal bleeding or

mild to severe bruising. **von Willebrand disease** and abnormalities in levels of factors V, VIII, XI, XII, and protein C (all proteins involved in clotting of blood) are common, alone or in combination. These problems may lessen as the person ages, even though the mentioned coagulation proteins may still be present in abnormal amounts. Rarely, some forms of leukemia and other cancers occur.

Kidney problems are often mild, but can occur. The most common finding is a widening of the pelvic (cup-shaped) cavity of the kidney. In males, smaller penis size and cryptorchidism are sometimes seen. Cryptorchidism may lead to improper sperm formation in these men, although sexual function is typically normal. It is not as common to see an affected man have a child with Noonan syndrome, and this is probably due to cryptorchidism. Puberty may be delayed in some women with NS1, but fertility is not usually compromised.

Lastly, follicular keratosis is common on the face and joints. It is a set of dark birthmarks that often show up during the first few months of life, typically along the eyebrows, eyes, cheeks, and scalp. Generally, it progresses until puberty, then stops. Sometimes it may leave scars, which may prevent hair growth in those areas. café-au-lait spots can occur, not unlike those seen in neurofibromatosis.

Diagnosis

As of 2001, there are no molecular or biochemical tests for Noonan syndrome, which would aid in confirming a diagnosis. Therefore, it is a clinical diagnosis, based on findings and symptoms. The challenge is that there are several conditions that mimic Noonan syndrome. If a female has symptoms, a chromosomal study is crucial to determine whether she has Turner syndrome, as she would have a missing X chromosome. Other chromosomal conditions that are similar include trisomy 8p (three copies of the small arm of chromosome 8) and trisomy 22 mosaicism (mixed cell lines with some having three copies of chromosome 22). A karyotype would help to rule these out.

An extremely similar condition is Cardio-facio-cutaneous syndrome (CFC), which has similar facial features, short stature, lymphedema, developmental delays, as well as similar heart defects and skin findings. It has been debated as to whether CFC and NS1 are the same condition. The most compelling argument that they are two, distinct condition lies with the fact that all cases of CFC are sporadic (meaning there is no family history), whereas NS1 may often be seen with a family history.

Other similar conditions include Watson and multiple lentigines/LEOPARD syndrome, as they are associated with pulmonary stenosis, wide-set eyes, chest deformities and mental delays. Careful study would identify Noonan syndrome from these.

Most individuals are diagnosed with NS1 in childhood, however some signs may present in late stages of a pregnancy. Lymphedema, cystic hygroma, and heart defects can sometimes be seen on a prenatal ultrasound. With high-resolution technology, occasionally some facial features may be seen as well. After such findings, an **amniocentesis** would typically be offered (as Turner syndrome would also be suspected) and a normal karyotype would further suspicion of NS1.

Treatment and management

Treatment is very symptom-specific, as not everyone will have the same needs. For short stature, some individuals have responded to growth hormone therapy. The exact cause of the short stature is not well defined, and therapies are currently being studied. Muscle weakness and early delays often necessitate an early intervention program, which combines physical, speech, and occupational therapies. Heart defects need to be closely followed, and treatment can sometimes include beta-blockers or surgeries, such as opening of the pulmonary valve. For individuals with clotting problems, aspirin and medications containing it should be avoided, as they prevent clotting. Treatments using various blood factors may be necessary to help with proper clotting. Drainage may be necessary for problematic lymphedema, but it is rare. Cryptorchidism may be surgically corrected, and testosterone replacement should be considered in males with abnormal sexual development. Back braces may be needed for scoliosis and other skeletal problems. Unfortunately, medications such as creams for the follicular keratosis are usually not helpful. Developmental delays should be assessed early, and special education classes may help with these. In summary, these various treatment modalities require careful coordination, and many issues are lifelong. A team approach may be beneficial.

Prognosis

Prognosis for Noonan syndrome is largely dependent on the extent of the various medical problems, particularly the heart defects. Individuals with a severe form of the condition may have a shorter life span than those with a milder presentation. In addition, presence of mental deficiency in 25% of individuals affects the long term prognosis.

Resources

ORGANIZATIONS

The Noonan Syndrome Support Group, Inc. c/o Mrs. Wanda Robinson, PO Box 145, Upperco, MD 21155.(888)

686-2224 or (410) 374-5245. andar@bellatlantic.net.
<http://www.noonansyndrome.org>.

WEBSITES

"Noonan Syndrome." *Ability.*
<http://www.ability.org.uk/Noonan_Syndrome.html>.

"Noonan Syndrome." *Family Village*.
<http://www.familyvillage.wisc.edu/lib_noon.htm

"Noonan Syndrome." *Pediatric Database*.
<http://www.icondata.com/health/pedbase/files/NOONANSY.HTM

Deepti Babu, MS

Norman-Landing disease *see* **GM1 gangliosidosis**

Norrie disease

Definition

Norrie disease (ND) is a severe form of blindness that is evident at birth or within the first few months of life and may involve deafness, mental retardation, and behavioral problems.

Description

ND was first described in the 1920s and 1930s as an inherited form of blindness affecting only males. Recognizable changes in certain parts of the eye were identified that lead to a wasting away or shrinking of the eye over time.

At birth, a grayish yellow, tumor-like mass is observed to cover or replace the retina of the eye, whereas the remainder of the eye is usually of normal shape, size, and form. Over time, changes in this mass and progressive deterioration of the lens, iris, and cornea cause the eye to appear milky in color and to become very small and shrunken. ND is always present in both eyes and although some abnormalities in the eye develop later, blindness is often present at birth. Some degree of mental retardation, behavior problems, and deafness may also occur.

ND is inherited in an X-linked recessive manner and so it affects only males. The **gene** for ND was found in the 1990s and **genetic testing** is available in the year 2001.

ND has also been referred to as:

- Norrie-Warburg syndrome
- Atrophia bulborum hereditaria
- Congenital progressive oculo-acoustico-cerebral degeneration
- Episkopi blindness
- Pseudoglioma congenita

Genetic profile

It has been known for several years by the analysis of many large families, that ND is an inherited condition that affects primarily males. Mothers of affected males do not show any symptoms of the disease. From this observation it was suspected that a gene on the X chromosome was responsible for the occurrence of ND. Genetic studies of many families led to the identification of a gene, named NDP (Norrie Disease Protein), located at Xp11. This means the gene is found on the shorter or upper arm of the X chromosome. NDP, a very small gene, was determined to produce a protein named norrin. The function of the norrin protein is not well understood. Preliminary evidence suggests that norrin plays a role in directing how cells interact and grow to become more specialized (differentiation).

Many different kinds of mistakes have been described in the NDP gene that are thought to lead to ND. The majority of these genetic mistakes or mutations alter a single unit of the genetic code and are called point mutations. Most of the identified point mutations are unique to the family studied. Few associations between the type of point mutation and severity of disease have been described. Other occasional errors in the NDP gene are called deletions, which permanently remove a portion of the genetic code from the gene. Individuals with deletions in the NDP gene are thought to have a more severe form of ND that usually includes profound mental retardation, seizures, small head size, and growth delays.

The X chromosome is one of the human sex **chromosomes**. A human being has 23 pairs of chromosomes in nearly every cell of their body. One of each kind (23) is inherited from the mother and another of each kind (23) is inherited from the father, which makes a total of 46. The twenty-third pair is the sex chromosome pair. Females have two X chromosomes and males have an X and a Y chromosome. Females therefore have two copies of all genes on the X chromosome but males have only one copy. The genes on the Y chromosome are different than those on the X chromosome. Mothers pass on either one of their X chromosomes to all of their children and fathers pass on their X chromosome to their daughters and their Y to their sons.

Males affected with ND have a mutation in their only copy of the NDP gene on their X chromosome and therefore do not make any normal norrin protein. Mothers of such affected males are usually carriers of

ND; they have one NDP gene with a mutation and one that is normal. As they have one normal copy of the NDP gene, they usually have a sufficient amount of the norrin protein so that they do not show signs of ND. Women that are carriers for ND have a 50% chance of passing the disease gene onto each of their children. If that child is male, he will be affected with ND. If that child is female, she will be a carrier of ND but not affected. Affected males that have children would pass on their disease gene to all of their daughters who would therefore be carriers of ND. Their sons inherit their Y chromosome and, therefore, would not inherit the gene for ND.

Genetic testing for mutations in the NDP gene is clinically available to help confirm a diagnosis of ND. As of the year 2001, this testing is able to identify gene mutations in about 70% of affected males. If such a mutation were found in an affected individual, accurate carrier testing would be available for females in that family. Additionally, diagnosis of a pregnancy could be offered to women who are at risk for having sons with ND.

Demographics

ND has been observed to affect males of many ethnic backgrounds and no ethnic group appears to predominate. The incidence is unknown, however.

Signs and symptoms

The first sign of ND is usually the reflection of a white area from within the eye, which gives the appearance of a white pupil. This is caused by a mass or growth behind the lens of the eye that covers the retina. This mass tends to grow and cause total blindness. It may also develop blood vessels that may burst and further damage the eye. At birth the iris, lens, cornea and globe of the eye are generally otherwise normal. The problems in the retina evolve over the first few months and until about ten years of age progressive changes in other parts of the eye develop. Cataracts form and the iris is observed to stick or be attached to the cornea and/or the lens of the eye. The iris will also often decrease in size. Pressure in the fluid within the eye may increase, which can be painful. The retina often becomes detached and may become thickened. Toward the end stages of the disease, the eye globe is seen to shrink considerably in size and appear sunken within the eye socket. The above findings affect both eyes and the changes are usually the same in each eye.

Approximately 50% of affected males have some degree of developmental delay or mental retardation. Some may show behavioral problems or psychosis-like features. Hearing loss may develop in 30–40% of males with ND starting in early childhood. If speech is developed before the onset of deafness, it is usually preserved. Mental impairment and hearing loss do not necessarily occur together. The role that the norrin protein plays in causing mental impairment and hearing loss is unknown.

Much variability in the expression of ND within a family as well as between families has been observed. On rare occasion, carrier females may show some of the retinal problems, such as retinal detachment, and may have some degree of vision loss.

KEY TERMS

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

Cochlea—A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

Cornea—The transparent structure of the eye over the lens that is continous with the sclera in forming the outermost, protective, layer of the eye.

Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Lens—The transparent, elastic, curved structure behind the iris (colored part of the eye) that helps focus light on the retina.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Diagnosis

The diagnosis of ND is usually made by clinical examination of the eye by a specialist called an ophthalmologist. Gene testing can be pursued as well, keeping in mind that as many as 30% of affected males cannot be identified using current methods.

The symptoms of ND have considerable overlap with a few other eye diseases and ND must be distinguished from the following conditions:

- Persistent hyperplastic primary vitreous (PHPV)
- Familial exudative vitroeretinopathy (FEVR)
- Retinoblastoma (RB)
- Retinopathy of prematurity (ROP)

- Incontinentia pigmenti type 2 (IP2) The first two diseases have been shown to also be associated with mutations in the NDP gene and may represent a more mild condition in the broad spectrum of ND.

Treatment and management

Since the symptoms of ND are often present at birth, little can be done to change them or prevent the disease from progressing. If the retina is still attached to the back of the eye, surgery or laser therapy may be helpful. An ophthalmologist should follow all children with ND to monitor the changes in the disease, including the pressure within the eye. Occasionally, surgery may be necessary. Rarely, the eye is removed because of pain.

The child's hearing should also be monitored regularly so that deafness can be detected early. For individuals with hearing loss, hearing aids are usually quite successful. Cochlear implants may be considered when hearing aids are not helpful in restoring hearing.

Developmental delays or mental retardation as well as lifelong behavioral problems can be a continuous challenge. Educational intervention and therapies may be helpful and can maximize a person's educational potential.

Prognosis

The lifespan of an individual with ND may be within the normal range. Risks associated with deafness, blindness, and mental retardation, including injury or illness, might shorten the lifespan. General health, however, is normal.

Resources

ORGANIZATIONS

American Council of the Blind. 1155 15th St. NW, Suite 720, Washington, DC 20005. (202) 467-5081 or (800) 424-8666. <http://www.acb.org>.

American Society for Deaf Children. PO Box 3355, Gettysburg, PA 17325. (800) 942-ASDC or (717) 334-7922 v/tty. <http://www.deafchildren.org/asdc2k/home/home.shtml>.

National Association of the Deaf. 814 Thayer, Suite 250, Silver Spring, MD 20910-4500. (301) 587-1788. nadinfo @nad.org. <http://www.nad.org>.

National Federation for the Blind. 1800 Johnson St., Baltimore, MD 21230. (410) 659-9314. epc@roundley.com. <http://www.nfb.org>.

Norrie Disease Association. Massachusetts General Hospital, E #6217, 149 13th St., Charlestown, MA 02129. (617) 726-5718. sims@helix.mgh.harvard.edu.

WEBSITES

Sims, Katherine B., MD. "Norrie Disease." [July 19, 1999]. *GeneClinics*. University of Washington, Seattle. <http://www.geneclinics.org/profiles/norrie/details.html>.

Jennifer Elizabeth Neil, MS, CGC

O

Obesity-hypotonia syndrome *see* **Cohen syndrome**

Oculo-auriculo-vertebral spectrum *see* **Goldenhar syndrome**

Oculocerebrorenal syndrome of Lowe *see* **Lowe syndrome**

Oculo-digito-esophago-duodenal syndrome

Definition

Oculo-digito-esophago-duodenal syndrome (ODED) is a rare genetic disorder characterized by multiple conditions including various hand and foot abnormalities, small head (microcephaly), incompletely formed esophagus and small intestine (esophageal/duodenal atresia), an extra eye fold (short palpebral fissures), and learning disabilities.

Description

Individuals diagnosed with oculo-digito-esophago-duodenal syndrome usually have a small head (microcephaly), fused toes (syndactyly), shortened fingers (mesobrachyphalangy), permanently outwardly curved fingers (clinodactyly), an extra eyelid fold (palpebral fissures), and learning delays. Other features can include backbone abnormalities (vertebral anomalies), an opening between the esophagus and the windpipe (tracheoesophageal fistula), and/or an incompletely formed esophagus or intestines (esophageal or duodenal atresia). The syndrome was first described by Dr. Murray Feingold in 1975. The underlying cause of the different features of ODED is not fully understood. ODED is also known as Feingold syndrome, Microcephaly, mental retardation, and tracheoesophageal fistula syndrome, and Microcephaly, Mesobrachyphalangy, Microcephaly-oculo-digito-esophago-duodenal (MODED) syndrome, Tracheo-esophagael fistula syndrome (MMT syndrome).

Genetic profile

The genetic cause of oculo-digito-esophago-duodenal syndrome is not fully understood. One study published in 2000 located an inherited region on the short arm of chromosome 2 that appears to cause ODED when mutated. However, it is still not clear if the features of ODED are caused by a single mutation in one **gene** or the deletion of several side-by-side genes (contiguous genes). Additionally, since this study is the first published molecular genetic study that has determined a specific location for ODED, it is unknown if most cases of ODED are caused by a mutation in this area or if ODED can be caused by genes at other locations as well.

Although the specific location and cause of ODED is not fully determined, it is known that ODED is inherited in families through a specific autosomal dominant pattern. Every individual has approximately 30,000-35,000 genes which tell their bodies how to form and function. Each gene is present in pairs, since one is inherited from their mother and one is inherited from their father. In an autosomal dominant condition, only one non-working copy of the gene for a particular condition is necessary for a person to experience symptoms of the condition. If a parent has an autosomal dominant condition, there is a 50% chance for each child to have the same or similar condition. Thus, individuals inheriting the same non-working gene in the same family can have very different symptoms. For example, approximately 28% of individuals affected by ODED have esophageal or duodenal atresia while hand anomalies are present in almost 100% of affected individuals. The difference in physical findings within the same family is known as variable penetrance or intrafamilial variability.

KEY TERMS

Contiguous gene syndrome—A genetic syndrome caused by the deletion of two or more genes located next to each other.

Variable penetrance—A term describing the way in which the same mutated gene can cause symptoms of different severity and type within the same family.

Demographics

Oculo-digito-esophago-duodenal syndrome is a rare genetic condition. As of 2000, only 90 patients affected by ODED have been reported in the literature. However, scientists believe that ODED has not been diagnosed in many affected individuals and suggest that ODED is more common than previously thought. The ethnic origin of individuals affected by ODED is varied and is not specific to any one country or group.

Signs and symptoms

The signs and symptoms of oculo-digito-esophago-duodenal syndrome vary from individual to individual. Most (86-94%) individuals diagnosed with ODED have a small head (microcephaly) and finger anomalies such as shortened fingers (mesobrachyphalangy), permanently curved fingers (clinodactyly), and/or missing fingers. Over half of affected individuals also have fused toes (syndactyly). Between 45% and 85% of individuals affected by ODED have developmental delays and/or mental retardation. Other features can include an extra eyelid fold (palpebral fissures), ear abnormalities/hearing loss, kidney abnormalities, backbone abnormalities (vertebral anomalies), an opening between the esophagus and the windpipe (tracheoesophageal fistula) and/or an incompletely formed esophagus, or intestines (duodenal atresia seen in 20-30%).

Diagnosis

Diagnosis of oculo-digito-esophago-duodenal syndrome is usually made following a physical exam by a medical geneticist using x rays of the hands, feet, and back.

Prenatal diagnosis of ODED can sometimes be made using serial, targeted level II ultrasound imaging, a technique that can provide pictures of the fetal head size, hands, feet, and digestive tract. Ultrasound results indicative of ODED include a “double bubble” sign suggesting incompletely formed intestines (duodenal atresia) and small head size (microcephaly). Diagnosis by ultrasound before the baby is born is difficult. Prenatal molecular **genetic testing** is not available as of 2001.

Treatment and management

Since oculo-digito-esophago-duodenal syndrome is a genetic disorder, no specific treatment is available to remove, cure, or fix all conditions associated with the disorder. Treatment for ODED is mainly limited to the treatment of specific symptoms. Individuals with incompletely formed intestinal and esophageal tracts would need immediate surgery to try and extend and open the digestive tract. Individuals with learning difficulties or mental retardation may benefit from special schooling and early intervention programs to help them learn and reach their potential.

Prognosis

Oculo-digito-esophago-duodenal syndrome results in a variety of different physical and mental signs and symptoms. Accordingly, the prognosis for each affected individual is very different.

Individuals who are affected by physical hand, head, or foot anomalies (with no other physical or mental abnormalities) have an excellent prognosis and most live normal lives.

Babies affected by ODED who have incomplete esophageal or intestinal tracts will have many surgeries and prognosis depends on the severity of the defect and survival of the surgeries.

Resources

BOOKS

Children with Hand Differences: A Guide for Families. Area Child Amputee Center Publications. Center for Limb Differences in Grand Rapids, MI, phone: 616-454-4988.

PERIODICALS

Piersall, L. D., et al. “Vertebral anomalies in a new family with ODED syndrome.” *Clinical Genetics* 57 (2000): 444-4448.

ORGANIZATIONS

Cherub Association of Families & Friends of Limb Disorder Children. 8401 Powers Rd., Batavia, NY 14020. (716) 762-9997.

EA/TEF Child and Family Support Connection, Inc. 111 West Jackson Blvd., Suite 1145, Chicago, IL 60604-3502. (312) 987-9085. Fax: (312) 987-9086. eatef2@aol.com. <http://www.eatef.org/>.

WEBSITES

OMIM—Online Mendelian Inheritance of Man. <http://www3.ncbi.nlm.nih.gov/Omim/>.

Reach. <http://www.reach.org.uk>.
The Family Village. <http://www.familyvillage.wisc.edu>.

Dawn A. Jacob, MS

Okihiro syndrome *see* **Duane retraction syndrome**

Olfactogenitalis of DeMorsier *see* **Kallmann syndrome**

Oligohydramnios sequence

Definition

Oligohydramnios sequence occurs as a result of having very little or no fluid (called amniotic fluid) surrounding a developing fetus during a pregnancy. "Oligohydramnios" means that there is less amniotic fluid present around the fetus than normal. A "sequence" is a chain of events that occurs as a result of a single abnormality or problem. Oligohydramnios sequence is therefore used to describe the features that a fetus develops as a result of very low or absent amount of amniotic fluid. In 1946, Dr. Potter first described the physical features seen in oligohydramnios sequence. Because of his description, oligohydramnios sequence has also been known as Potter syndrome or Potter sequence.

Description

During a pregnancy, the amount of amniotic fluid typically increases through the seventh month and then slightly decreases during the eighth and ninth months. During the first 16 weeks of the pregnancy, the mother's body produces the amniotic fluid. At approximately 16 weeks, the fetal kidneys begin to function, producing the majority of the amniotic fluid from that point until the end of the pregnancy. The amount of amniotic fluid, as it increases, causes the space around the fetus (amniotic cavity) to expand, allowing enough room for the fetus to grow and develop normally.

Oligohydramnios typically is diagnosed during the second and/or third trimester of a pregnancy. When the oligohydramnios is severe enough and is present for an extended period of time, oligohydramnios sequence tends to develop. There are several problems that can cause oligohydramnios to occur. Severe oligohydramnios can develop when there are abnormalities with the fetal renal system or when there is a constant leakage of amniotic fluid. Sometimes, the cause of the severe oligohydramnios is unknown.

Approximately 50% of the time, fetal renal system abnormalities cause the severe oligohydramnios, resulting in the fetus developing oligohydramnios sequence. This is because if there is a problem with the fetal renal system, there is the possibility that not enough amniotic fluid is being produced. Renal system abnormalities that have been associated with the development of oligohydramnios sequence include, the absence of both kidneys (renal agenesis), bilateral cystic kidneys, absence of one kidney with the other kidney being cystic, and obstructions that blocks the urine from exiting the renal system. In a fetus affected with oligohydramnios sequence, sometimes the renal system abnormality is the only abnormality the fetus has. However, approximately 54% of fetuses with oligohydramnios sequence due to a renal system abnormality will have other birth defects or differences with their growth and development. Sometimes the presence of other abnormalities indicates that the fetus may be affected with a syndrome or condition in which a renal system problem can be a feature. Renal system abnormalities in a fetus can also be associated with certain maternal illnesses, such as insulin dependant **diabetes mellitus**, or the use of certain medications during a pregnancy.

Severe oligohydramnios can also develop even when the fetal renal system appears normal. In this situation, often the oligohydramnios occurs as the result of chronic leakage of amniotic fluid. Chronic leakage of amniotic fluid can result from an infection or prolonged premature rupture of the membranes that surround the fetus (PROM). In chronic leakage of amniotic fluid, the fetus still produces enough amniotic fluid, however, there is an opening in the membrane surrounding the fetus, causing the amniotic fluid to leak out from the amniotic cavity.

Genetic profile

The chance for oligohydramnios sequence to occur again in a future pregnancy or in a family member's pregnancy is dependant on the underlying problem or syndrome that caused the oligohydramnios sequence to develop. There have been many fetuses affected with oligohydramnios sequence where the underlying cause of the severe oligohydramnios has been a genetic abnormality. However, not all causes of severe oligohydramnios that result in the development of oligohydramnios sequence have a genetic basis. The genetic abnormalities that have caused oligohydramnios developing during a pregnancy include a single **gene** change, a missing gene, or a chromosome anomaly.

KEY TERMS

Anomaly—Different from the normal or expected. Unusual or irregular structure.

Bilateral—Relating to or affecting both sides of the body or both of a pair of organs.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term embryo is used prior to the third month.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Renal system—The organs involved with the production and output of urine.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

Teratogen—Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

Unilateral—Refers to one side of the body or only one organ in a pair.

Although some fetuses with oligohydramnios sequence have been found to have a chromosome anomaly, the likelihood that a chromosome anomaly is the underlying cause of the renal system anomaly or other problem resulting in the severe oligohydramnios is low. A chromosome anomaly can be a difference in the total number of **chromosomes** a fetus has (such as having an extra or missing chromosome), a missing piece of a chromosome, an extra piece of a chromosome, or a rearrangement of the chromosomal material. Some of the chromosome anomalies can occur for the first time at the conception of the fetus (sporadic), while other chromosome anomalies can be inherited from a parent. Both sporadic and inherited chromosome anomalies have been seen in fetuses with oligohydramnios sequence. The chance for a chromosome anomaly to occur again in a family is dependent on the specific chromosome anomaly. When the chromosome anomaly is considered to be sporadic, the chance for chromosome anomaly to occur again in a pregnancy is 1% added to the mother's age-related risk to have a baby with a chromosome anomaly. If the chromosome anomaly (typically a rearrangement of chromosomal material) was inherited from a parent, the recurrence risk would be based on the specific chromosome arrangement involved. However, even if a chromosome anomaly were to recur in a future pregnancy, it does not necessarily mean that the fetus would develop oligohydramnios that could cause the development of oligohydramnios sequence.

Many of the genetic conditions that can cause oligohydramnios sequence are inherited in an autosomal recessive manner. An autosomal recessive condition is caused by a difference in a gene. Like chromosomes, the genes also come in pairs. An autosomal recessive condition occurs when both genes in a pair don't function properly. Typically, genes don't function properly because there is a change within the gene causing it not to work or because the gene is missing. An individual has an autosomal recessive condition when they inherit one non-working gene from their mother and the same non-working gene from their father. These parents are called "carriers" for that condition. Carriers of a condition typically do not exhibit any symptoms of that condition. With autosomal recessive **inheritance**, when two carriers for the same condition have a baby, there is a 25% chance for that baby to inherit the condition. There are several autosomal recessive conditions that can cause fetal renal abnormalities potentially resulting in the fetus to develop oligohydramnios sequence.

Oligohydramnios sequence has also been seen in some fetuses with an autosomal dominant conditions. An autosomal dominant condition occurs when only one gene in a pair does not function properly or is missing. This non-working gene can either be inherited from a parent or occur for the first time at conception. There are many autosomal dominant conditions where affected family members have different features and severity of the same condition. If a fetus is felt to have had oligohydramnios sequence that has been associated with an autosomal dominant condition, it would have to be determined if the condition was inherited from a parent or occurred for the first time. If the condition was inherited from a parent, that parent would have a 50% chance of passing the condition on with each future pregnancy.

Sometimes the fetus with oligohydramnios sequence has a condition or syndrome that is known to occur sporadically. Sporadic conditions are conditions that tend to occur once in a family and the pattern of inheritance is unknown. Since there are some families where a sporadic condition has occurred more than one time, a recurrence risk of approximately 1% or less is often given to families where only one pregnancy has been affected with a sporadic condition.

Sometimes examinations of family members of an affected pregnancy can help determine the exact diagnosis and pattern of inheritance. It is estimated that approximately 9% of first-degree relatives (parent, brother, or sister) of a fetus who developed oligohydramnios sequence as a result of a renal abnormality, will also have renal abnormalities that do not cause any problems or

symptoms. It is important to remember that if a pregnancy inherits a condition that is associated with oligohydramnios sequence, it does not necessarily mean that the pregnancy will develop oligohydramnios sequence. Therefore, for each subsequent pregnancy, the risk is related to inheriting the condition or syndrome, not necessarily to develop oligohydramnios sequence.

Demographics

There is no one group of individuals or one particular sex that have a higher risk to develop oligohydramnios sequence. Although, some of the inherited conditions that have been associated with oligohydramnios sequence may be more common in certain regions of the world or in certain ethnic groups.

Signs and symptoms

With severe oligohydramnios, because of the lack of amniotic fluid, the amniotic cavity remains small, thereby constricting the fetus. As the fetus grows, the amniotic cavity tightens around the fetus, inhibiting normal growth and development. This typically results in the formation of certain facial features, overall small size, wrinkled skin, and prevents the arms and legs from moving.

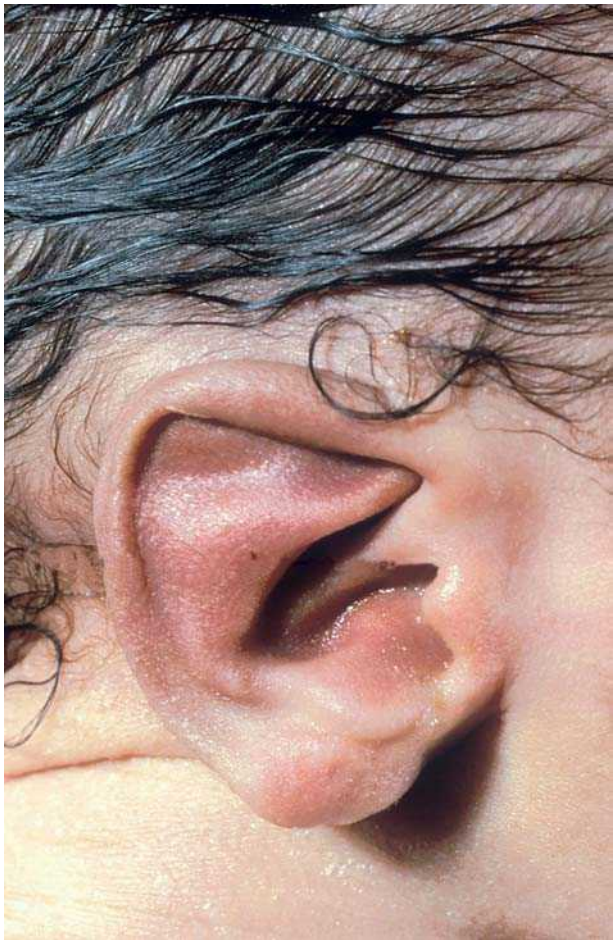
The facial features seen in oligohydramnios sequence include a flattened face, wide-set eyes, a flattened, beaked nose, ears set lower on the head than expected (low-set ears), and a small, receding chin (micrognathia).

Because the movement of the arms and legs are restricted, a variety of limb deformities can occur, including bilateral **clubfoot** (both feet turned to the side), dislocated hips, broad flat hands and joint contractures (inability for the joints to fully extend). Contractures tend to be seen more often in fetuses where the oligohydramnios occurred during the second trimester. Broad, flat hands tend to be seen more often in fetuses where the oligohydramnios began during the third trimester.

Fetuses with oligohydramnios sequence also tend to have pulmonary hypoplasia (underdevelopment of the lungs). The pulmonary hypoplasia is felt to occur as a result of the compression of the fetal chest (thorax), although it has been suggested that pulmonary hypoplasia may develop before 16 weeks of pregnancy in some cases. Therefore, regardless of the cause of the severe oligohydramnios, the physical features that develop and are seen in oligohydramnios sequence tend to be the same.

Diagnosis

An ultrasound examination during the second and/or third trimester of a pregnancy is a good tool to help detect the presence of oligohydramnios. Since oligohydramnios can occur later in a pregnancy, an ultrasound examination performed during the second trimester may not detect the presence of oligohydramnios. In pregnancies affected with oligohydramnios, an ultrasound examination can be difficult to perform because there is less amniotic fluid around the fetus. Therefore, an ultrasound examination may not be able to detect the underlying cause of the oligohydramnios.



Low set ears are a common feature of infants with olioghydramnios sequence. *(Custom Medical Stock Photo, Inc.)*

In some situations, an amnioinfusion (injection of fluid into the amniotic cavity) is performed. This can sometimes help determine if the cause of the oligohydramnios was leakage of the amniotic fluid. Amnioinfusions may also be used to help visualize the fetus on ultrasound in attempts to detect any fetal abnormalities.

Additionally, maternal serum screening may detect the presence of oligohydramnios in a pregnancy. Maternal serum screening is a blood test offered to preg-

nant women to help determine the chance that their baby may have **Down syndrome**, **Trisomy 18**, and **spina bifida**. This test is typically performed between the fifteenth and twentith week of a pregnancy. The test works by measuring amount of certain substances in the maternal circulation.

Alpha-fetoprotein (AFP) is a protein produced mainly by the fetal liver and is one of the substances measured in the mother's blood. The level of AFP in the mother's blood has been used to help find pregnancies at higher risk to have spina bifida. An elevated AFP in the mother's blood, which is greater than 2.5 multiples of the median (MoM), has also been associated with several conditions, including the presence of oligohydramnios in a pregnancy. Since oligohydramnios is just one of several explanations for an elevated AFP level, an ultrasound examination is recommended when there is an elevated AFP level. However, not all pregnancies affected with oligohydramnios will have an elevated AFP level, some pregnancies with oligohydramnios will have the AFP level within the normal range.

Because fetuses with oligohydramnios sequence can have other anomalies, a detailed examination of the fetus should be performed. Knowing all the abnormalities a fetus has is important in making an accurate diagnosis. Knowing the cause of the oligohydramnios and if it is related to a syndrome or genetic condition is essential in predicting the chance for the condition to occur again in a future pregnancy. Sometimes the fetal abnormalities can be detected on a prenatal ultrasound examination or on an external examination of the fetus after delivery. However, several studies have shown that an external examination of the fetus can miss some fetal abnormalities and have stressed the importance of performing an autopsy to make an accurate diagnosis.

Treatment and management

There is currently no treatment or prevention for oligohydramnios sequence. Amnioinfusions, which can assist in determining the cause of the oligohydramnios in a pregnancy, is not recommended as a treatment for oligohydramnios sequence.

Prognosis

Pregnancies affected with oligohydramnios sequence can miscarry, be stillborn, or die shortly after birth. This condition is almost always fatal because the lungs do not develop completely (pulmonary hypoplasia).

Resources

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Sharon A. Aufox, MS, CGC

Ollier disease *see* **Chondrosarcoma**

Omphalocele

Definition

An omphalocele occurs when the abdominal wall does not close properly during fetal development. The extent to which abdominal contents protrude through the base of the umbilical cord will vary. A membrane usually covers the defect.

Description

An omphalocele is an abnormal closure of the abdominal wall. Between the sixth and tenth weeks of pregnancy, the intestines normally protrude into the umbilical cord as the baby is developing. During the tenth week, the intestines should return and rotate in such a way that the abdomen is closed around the umbilical cord. An omphalocele occurs when the intestines do not return, and this closure does not occur properly.

Genetic profile

In one-third of infants, an omphalocele occurs by itself, and is said to be an isolated abnormality. The cause

of an isolated omphalocele is suspected to be multifactorial. Multifactorial means that many factors, both genetic and environmental, contribute to the cause. The specific genes involved, as well as the specific environmental factors are largely unknown. The chance for a couple to have another baby with an omphalocele, after they have had one with an isolated omphalocele is approximately one in 100 or 1%.

The remaining two-thirds of babies with an omphalocele have other birth defects, including problems with the heart (heart disease), spine (**spina bifida**), digestive system, urinary system, and the limbs.

Approximately 30% of babies with an omphalocele have a chromosome abnormality as the underlying cause of the omphalocele. Babies with chromosome abnormalities usually have multiple birth defects, so many babies will have other medical problems in addition to the omphalocele. **Chromosomes** are structures in the center of the cell that contain our genes; our genes code for our traits, such as blood type or eye color. The normal number of chromosomes is 46; having extra or missing chromosome material is associated with health problems. Babies with an omphalocele may have an extra chromosome number 13, 18, 21, or others. An omphalocele is sometimes said to occur more often in a mother who is older. This is because the chance for a chromosome abnormality to occur increases with maternal age.

Some infants with an omphalocele have a syndrome (collection of health problems). An example is **Beckwith-Wiedemann syndrome**, where a baby is born larger than normal (macrosomia), has an omphalocele, and a large tongue (macroglossia). Finally, in some families, an omphalocele has been reported to be inherited as an autosomal dominant, or autosomal recessive trait. Autosomal means that males and females are equally affected. Dominant means that only one **gene** is necessary to produce the condition, while recessive means that two genes are necessary to have the condition. With autosomal dominant **inheritance**, there is a 50% chance with each pregnancy to have an affected child, while with autosomal recessive inheritance. the recurrence risk is 25%.

Demographics

Omphalocele is estimated to occur in one in 4,000 to one in 6,000 liveborns. Males are slightly more often affected than females (1.5:1).

Signs and symptoms

Anytime an infant is born with an omphalocele, a thorough physical examination is performed to determine whether the omphalocele is isolated or associated with other health problems. To determine this, various studies may be performed such as a chromosome study, which is done from a small blood sample. Since the chest cavity may be small in an infant born with an omphalocele, the baby may have underdeveloped lungs, requiring breathing assistance with a ventilator (mechanical breathing machine). In 10–20% of infants, the sac has torn (ruptured), requiring immediate surgical repair, due to the risk of infection.

Diagnosis

During pregnancy, two different signs may cause a physician to suspect an omphalocele: increased fluid around the baby (polyhydramnios) on a fetal ultrasound and/or an abnormal maternal serum screening test, showing an elevated amount of alpha-fetoprotein (AFP). Maternal serum screening, measuring analytes present in the mother's bloodstream only during pregnancy, is offered to pregnant women usually under the age of 35, to screen for various disorders such as **Down syndrome**, **trisomy 18**, and abnormalities of the spine (such as spina bifida). Other abnormalities can give an abnormal test result, and an omphalocele is an example.

An ultrasound is often performed as the first step when a woman's maternal serum screening is abnormal, if one has not already been performed. Omphalocele is usually identifiable on fetal ultrasound. If a woman's fetal ultrasound showed an omphalocele, polyhydramnios, or if she had an abnormal maternal serum screening test, an **amniocentesis** may be offered.

Amniocentesis is a procedure done under ultrasound guidance where a long thin needle is inserted into the mother's abdomen, then into the uterus, to withdraw a couple tablespoons of amniotic fluid (fluid surrounding the developing baby) to study. Measurement of the AFP in the amniotic fluid can then be done to test for problems such as omphalocele. In addition, a chromosome analysis for the baby can be performed on the cells contained in the amniotic fluid. When the AFP in the amniotic fluid is elevated, an additional test is used to look for the presence or absence of an enzyme found in nerve tissue, called acetylcholinesterase, or ACHE. ACHE is present in the amniotic fluid only when a baby has an opening such as spina bifida or an omphalocele. Not all babies with an omphalocele will cause the maternal serum screening test to be abnormal or to cause extra fluid accumulation, but many will. At birth, an omphalocele is diagnosed by visual/physical examination.

Treatment and management

Treatment and management of an omphalocele depends upon the size of the abnormality, whether the sac

KEY TERMS

Acetylcholinesterase (ACHE)—An enzyme found in nerve tissue.

Alpha-fetoprotein (AFP)—A chemical substance produced by the fetus and found in the fetal circulation. AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid which surrounds a developing baby during pregnancy.

Analyte—A chemical substance such as an enzyme, hormone, or protein.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Beckwith-Wiedemann syndrome—A collection of health problems present at birth including an omphalocele, large tongue, and large body size.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Gastroschisis—A small defect in the abdominal wall normally located to the right of the umbilicus, and not covered by a membrane, where intestines and other organs may protrude.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Macroglossia—A large tongue.

Macrosomia—Overall large size due to overgrowth.

Maternal serum screening—A blood test offered to pregnant women usually under the age of 35, which measures analytes in the mother's blood that are present only during pregnancy, to screen for Down syndrome, trisomy 18, and neural tube defects.

Multifactorial—Describes a disease that is the product of the interaction of multiple genetic and environmental factors.

Omphalocele—A birth defect where the bowel and sometimes the liver, protrudes through an opening in the baby's abdomen near the umbilical cord.

Polyhydramnios—A condition in which there is too much fluid around the fetus in the amniotic sac.

Thoracic cavity—The chest.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Ventilator—Mechanical breathing machine.

Ventral wall defect—An opening in the abdomen (ventral wall). Examples include omphalocele and gastroschisis.

is intact or ruptured, and whether other health problems are present. A small omphalocele is usually repaired by surgery shortly after birth, where an operation is performed to return the organs to the abdomen and close the opening in the abdominal wall. If the omphalocele is large, where most of the intestines, liver, and/or spleen are present outside of the body, the repair is done in stages because the abdomen is small and may not be able to hold all of the organs at once. Initially, sterile protective gauze is placed over the abdominal organs whether the omphalocele is large or small. The exposed organs are then gradually moved back into the abdomen over several days or weeks. The abdominal wall is surgically closed once all of the organs have been returned to the abdomen. Infants are often on a breathing machine (ventilator) until the abdominal cavity increases in size since returning the organs to the abdomen may crowd the lungs in the chest area.

Prognosis

The prognosis of an infant born with an omphalocele depends upon the size of the defect, whether there was a loss of blood flow to part of the intestines or other organs,

and the extent of other abnormalities. The survival rate overall for an infant born with an isolated omphalocele has improved greatly over the past forty years, from 60% to over 90%.

Resources

ORGANIZATIONS

Foundation for Blood Research. PO Box 190, 69 US Route One, Scarborough, ME 04070-0190. (207) 883-4131. Fax: (207) 883-1527. <http://www.fbr.org>.

WEBSITES

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Catherine L. Tesla, MS, CGC

Oncogene

Definition

In a cell with normal control regulation (non-cancerous), genes produce proteins that provide regulated cell division. **Cancer** is the disease caused by cells that have lost their ability to control their regulation. The abnormal proteins allowing the non-regulated cancerous state are produced by genes known as oncogenes. The normal **gene** from which the oncogene evolved is called a proto-oncogene.

Description

History

The word oncogene comes from the Greek term *oncos*, which means tumor. Oncogenes were originally discovered in certain types of animal viruses that were capable of inducing tumors in the animals they infected. These viral oncogenes, called v-onc, were later found in human tumors, although most human cancers do not appear to be caused by viruses. Since their original discovery, hundreds of oncogenes have been found, but only a small number of them are known to affect humans. Although different oncogenes have different functions, they are all somehow involved in the process of transformation (change) of normal cells to cancerous cells.

The transformation of normal cells into cancerous cells

The process by which normal cells are transformed into cancerous cells is a complex, multi-step process involving a breakdown in the normal cell cycle. Normally, a somatic cell goes through a growth cycle in which it produces new cells. The two main stages of this cycle are interphase (genetic material in the cell duplicates) and mitosis (the cell divides to produce two other identical cells). The process of cell division is necessary for the growth of tissues and organs of the body and for the replacement of damaged cells. Normal cells have a limited life span and only go through the cell cycle a limited number of times.

Different cell types are produced by the regulation of which genes in a given cell are allowed to be expressed. One way cancer is caused, is by de-regulation of those genes related to control of the cell cycle; the development of oncogenes. If the oncogene is present in a skin cell, the patient will have skin cancer; in a breast cell, **breast cancer** will result, and so on.

Cells that loose control of their cell cycle and replicate out of control are called cancer cells. Cancer cells undergo many cell divisions often at a quicker rate than normal cells and do not have a limited life span. This allows them to eventually overwhelm the body with a large number of abnormal cells and eventually affect the functioning of the normal cells.

A cell becomes cancerous only after changes occur in a number of genes that are involved in the regulation of its cell cycle. A change in a regulatory gene can cause it to stop producing a normal regulatory protein or can produce an abnormal protein which does not regulate the cell in a normal manner. When changes occur in one regulatory gene this often causes changes in other regulatory genes. Cancers in different types of cells can be caused by changes in different types of regulatory genes.

Proto-oncogenes and tumor-suppressor genes are the two most common genes involved in regulating the cell cycle. Proto-oncogenes and tumor-suppressor genes have different functions in the cell cycle. Tumor-suppressor genes produce proteins that are involved in prevention of uncontrolled cell growth and division. Since two of each type of gene are inherited two of each type of tumor-suppressor gene are inherited. Both tumor suppressor genes of a pair need to be changed in order for the protein produced to stop functioning as a tumor suppressor. Mutated tumor-suppressor genes therefore act in an autosomal recessive manner.

Proto-oncogenes produce proteins that are largely involved in stimulating the growth and division of cells in a controlled manner. Each proto-oncogene produces a different protein that has a unique role in regulating the cell cycles of particular types of cells. We inherit two of each type of proto-oncogene. A change in only one proto-oncogene of a pair converts it into an oncogene. The

oncogene produces an abnormal protein, which is somehow involved in stimulating uncontrolled cell growth. An oncogene acts in an autosomal dominant manner since only one proto-oncogene of a pair needs to be changed in the formation of an oncogene.

Classes of proto-oncogene

There are five major classes of proto-oncogene/oncogenes: (1) growth factors, (2) growth factor receptors, (3) signal transducers (4) transcription factors, and (5) programmed cell death regulators.

GROWTH FACTORS Some proto-oncogenes produce proteins, called growth factors, which indirectly stimulate growth of the cell by activating receptors on the surface of the cell. Different growth factors activate different receptors, found on different cells of the body. Mutations in growth factor proto-oncogene result in oncogenes that promote uncontrolled growth in cells for which they have a receptor. For example, platelet-derived growth factor (PDGF) is a proto-oncogene that helps to promote wound healing by stimulating the growth of cells around a wound. PDGF can be mutated into an oncogene called v-sis (PDGFB) which is often present in connective-tissue tumors.

GROWTH FACTOR RECEPTORS Growth factor receptors are found on the surface of cells and are activated by growth factors. Growth factors send signals to the center of the cell (nucleus) and stimulate cells that are at rest to enter the cell cycle. Different cells have different growth factors receptors. Mutations in a proto-oncogene that are growth factor receptors can result in oncogenes that produce receptors that do not require growth factors to stimulate cell growth. Overstimulation of cells to enter the cell cycle can result and promote uncontrolled cell growth. Most proto-oncogene growth factor receptors are called tyrosine kinases and are very involved in controlling cell shape and growth. One example of a tyrosine kinase is called GDFNR. The RET (rearranged during transfection) oncogene is a mutated form of GDFNR and is commonly found in cancerous thyroid cells.

SIGNAL TRANSDUCERS Signal transducers are proteins that relay cell cycle stimulation signals, from growth factor receptors to proteins in the nucleus of the cell. The transfer of signals to the nucleus is a stepwise process that involves a large number of proto-oncogenes and is often called the signal transduction cascade. Mutations in proto-oncogene involved in this cascade can cause unregulated activity, which can result in abnormal cell proliferation. Signal transducer oncogenes are the largest class of oncogenes. The RAS family is a group of 50 related signal transducer oncogenes that are found in approximately 20% of tumors.

TRANSCRIPTION FACTORS Transcription factors are proteins found in the nucleus of the cell which ultimately receive the signals from the growth factor receptors. Transcription factors directly control the expression of genes that are involved in the growth and proliferation of cells. Transcription factors produced by oncogenes typically do not require growth factor receptor stimulation and thus can result in uncontrolled cell proliferation. Transcription factor proto-oncogenes are often changed into oncogenes by chromosomal translocations in leukemias, lymphomas, and solid tumors. C-myc is a common transcription factor oncogene that results from a chromosomal translocation and is often found in leukemias and lymphomas.

PROGRAMMED CELL DEATH REGULATORS Normal cells have a predetermined life span and different genes regulate their growth and death. Cells that have been damaged or have an abnormal cell cycle may develop into cancer cells. Usually these cells are destroyed through a process called programmed cell death (apoptosis). Cells that have developed into cancer cells, however, do not undergo apoptosis. Mutated proto-oncogenes may inhibit the death of abnormal cells, which can lead to the formation and spread of cancer. The bcl-2 oncogene, for example, inhibits cell death in cancerous cells of the immune system.

Mechanisms of transformation of proto-oncogene into oncogenes

It is not known in most cases what triggers a particular proto-oncogene to change into an oncogene. There appear to be environmental triggers such as exposure to toxic chemicals. There also appear to be genetic triggers since changes in other genes in a particular cell can trigger changes in proto-oncogenes.

The mechanisms through which proto-oncogenes are changed into oncogenes are, however, better understood. Proto-oncogenes are transformed into oncogenes through: 1) mutation 2) chromosomal translocation, and 3) gene amplification.

A tiny change, called a mutation, in a proto-oncogene can convert it into an oncogene. The mutation results in an oncogene that produces a protein with an abnormal structure. These mutations often make the protein resistant to regulation and cause uncontrolled and continuous activity of the protein. The RAS family of oncogenes, found in approximately 20% of tumors, are examples of oncogenes caused by mutations.

Chromosomal translocations, which result from errors in mitosis, have also been implicated in the transformation of proto-oncogenes into oncogenes. Chromosomal translocations result in the transfer of a

KEY TERMS

Autosomal dominant manner—An abnormal gene on one of the 22 pairs of non-sex chromosomes that will display the defect when only one copy is inherited.

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Leukemia—Cancer of the blood forming organs which results in an overproduction of white blood cells.

Lymphoma—A malignant tumor of the lymph nodes.

Mitosis—The process by which a somatic cell—a cell not destined to become a sperm or egg—duplicates its chromosomes and divides to produce two new cells.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nucleus—The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

Parathyroid glands—A pair of glands adjacent to the thyroid gland that primarily regulate blood calcium levels.

Pheochromocytoma—A small vascular tumor of the inner region of the adrenal gland. The tumor causes uncontrolled and irregular secretion of certain hormones.

Proliferation—The growth or production of cells.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Proto-oncogene—A gene involved in stimulating the normal growth and division of cells in a controlled manner.

Replicate—Produce identical copies of itself.

Somatic cells—All the cells of the body except for the egg and sperm cells.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Tumor suppressor gene—Genes involved in controlling normal cell growth and preventing cancer.

proto-oncogene from its normal location on a chromosome to a different location on another chromosome. Sometimes this translocation results in the transfer of a proto-oncogene next to a gene involved in the immune system. This results in an oncogene that is controlled by the immune system gene and as a result becomes deregulated. One example of this mechanism is the transfer of the c-myc proto-oncogene from its normal location on chromosome 8 to a location near an immune system gene on chromosome 14. This translocation results in the deregulation of c-myc and is involved in the development of Burkitt's lymphoma. The translocated c-myc proto-oncogene is found in the cancer cells of approximately 85% of people with Burkitt's lymphoma.

In other cases, the translocation results in the fusion of a proto-oncogene with another gene. The resulting oncogene produces an unregulated protein that is involved in stimulating uncontrolled cell proliferation. The first discovered fusion oncogene resulted from a Philadelphia chromosome translocation. This type of translocation is found in the leukemia cells of greater than 95% of patients with a chronic form of leukemia. The Philadelphia chromosome translocation results in the fusion of the c-abl proto-oncogene, normally found on chromosome 9 to the bcr gene found on chromosome 22. The fused gene produces an unregulated transcription factor protein that has a different structure than the normal protein. It is not

known how this protein contributes to the formation of cancer cells.

Some oncogenes result when multiple copies of a proto-oncogene are created (gene amplification). Gene amplification often results in hundreds of copies of a gene, which results in increased production of proteins and increased cell growth. Multiple copies of proto-oncogenes are found in many tumors. Sometimes amplified genes form separate **chromosomes** called double minute chromosomes and sometimes they are found within normal chromosomes.

Inherited oncogenes

In most cases, oncogenes result from changes in proto-oncogenes in select somatic cells and are not passed on to future generations. People with an inherited oncogene, however, do exist. They possess one changed proto-oncogene (oncogene) and one unchanged proto-oncogene in all of their somatic cells. The somatic cells have two of each chromosome and therefore two of each gene since one of each type of chromosome is inherited from the mother in the egg cell and one of each is inherited from the father in the sperm cell. The egg and sperm cells have undergone a number of divisions in their cell cycle and therefore only contain one of each type of chromosome and one of each type of gene. A person with an inherited oncogene has a changed proto-oncogene in approximately 50% of their egg or sperm cells and an unchanged proto-oncogene in the other 50% of their egg or sperm cells and therefore has a 50% chance of passing this oncogene on to their children.

A person only has to inherit a change in one proto-oncogene of a pair to have an increased risk of cancer. This is called autosomal dominant **inheritance**. Not all people with an inherited oncogene develop cancer, since mutations in other genes that regulate the cell cycle need to occur in a cell for it to be transformed into a cancerous cell. The presence of an oncogene in a cell does, however, make it more likely that changes will occur in other regulatory genes. The degree of cancer risk depends on the type of oncogene inherited as well as other genetic factors and environmental exposures. The type of cancers that are likely to develop depend on the type of oncogene that has been inherited.

Multiple endocrine neoplasia type II (MENII) is one example of a condition caused by an inherited oncogene. People with MENII have usually inherited the RET oncogene. They have approximately a 70% chance of developing thyroid cancer, a 50% chance of developing a tumor of the adrenal glands (pheochromocytoma) and about a 5-10% chance of developing symptomatic parathyroid disease.

Oncogenes as targets for cancer treatment

The discovery of oncogenes approximately 20 years ago has played an important role in developing an understanding of cancer. Oncogenes promise to play an even greater role in the development of improved cancer therapies since oncogenes may be important targets for drugs that are used for the treatment of cancer. The goal of these therapies is to selectively destroy cancer cells while leaving normal cells intact. Many anti-cancer therapies currently under development are designed to interfere with oncogenic signal transducer proteins, which relay the signals involved in triggering the abnormal growth of tumor cells. Other therapies hope to trigger specific oncogenes to cause programmed cell death in cancer cells. Whatever the mechanism by which they operate, it is hoped that these experimental therapies will offer a great improvement over current cancer treatments.

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Lisa Maria Andres, MS, CGC

Onychoosteodysplasia *see* **Nail-Patella syndrome**

Opitz syndrome

Definition

Opitz syndrome is a heterogeneous genetic condition characterized by a range of midline birth defects such as hypertelorism, clefts in the lips and larynx, heart defects, hypospadias and agenesis of the corpus callosum.

Description

Opitz syndrome or Opitz G/BBB syndrome, as it is sometimes called, includes G syndrome and BBB syndrome, which were originally thought to be two different syndromes. In 1969, Dr. John Opitz described two similar conditions that he called G syndrome and BBB syndrome. G syndrome was named after one family affected with this syndrome whose last name began with the initial G and BBB syndrome was named after the surname of three different families. Subsequent research suggested that these two conditions were one disorder but researchers could not agree on how this disorder was inherited. It wasn't until 1995 that Dr. Nathaniel Robin and his colleagues demonstrated that Opitz syndrome had both X-linked and autosomal dominant forms.

Opitz syndrome is a complex condition that has many symptoms, most of which affect organs along the midline of the body such as clefts in the lip and larynx, heart defects, hypospadias and agenesis of the corpus callosum. Opitz syndrome has variable expressivity, which means that different people with the disorder can have different symptoms. This condition also has decreased penetrance, which means that not all people who inherit this disorder will have symptoms.

Genetic profile

Opitz syndrome is a genetically heterogeneous condition. There appear to be at least two to three genes that can cause Opitz syndrome when changed (mutated) or deleted. Opitz syndrome can be caused by changes in genes found on the X chromosome (X-linked) and changes in or deletion of a **gene** found on chromosome 22 (autosomal dominant).

Chromosomes, genes, and proteins

Each cell of the body, except for the egg and sperm cells contain 23 pairs of chromosomes—46 **chromosomes** in total. The egg and sperm cells contain only one of each type of chromosome and therefore contain 23 chromosomes in total. Males and females have 22 pairs of chromosomes, called the autosomes, numbered one to twenty-two in order of decreasing size. The other pair of chromosomes, called the sex chromosomes, determines the sex of the individual. Women possess two identical chromosomes called the X chromosomes while men possess one X chromosome and one Y chromosome. Since every egg cell contains an X chromosome, women pass on the X chromosome to their daughters and sons. Some sperm cells contain an X chromosome and some sperm cells contain a Y chromosome. Men pass the X chromosome on to their daughters and the Y chromosome on to their sons. Each type of chromosome contains different genes that are found at specific locations along the chromosome. Men and women inherit two of each type of autosomal gene since they inherit two of each type of autosome. Women inherit two of each type of X-linked gene since they possess two X chromosomes. Men inherit only one of each X-linked gene since they posses only one X chromosome.

Each gene contains the instructions for the production of a particular protein. The proteins produced by genes have many functions and work together to create the traits of the human body such as hair and eye color and are involved in controlling the basic functions of the human body. Changes or deletions of genes can cause them to produce abnormal protein, less protein or no protein. This can prevent the protein from functioning normally.

Autosomal dominant Opitz syndrome

The gene responsible for the autosomal dominant form of Opitz syndrome has not been discovered yet, but it appears to result from a deletion in a segment of chromosome 22 containing the Opitz gene or a change in the gene responsible for Opitz syndrome. In some cases the deletion or gene change is inherited from either the mother or father who have the gene change or deletion in one chromosome 22 in their somatic cells. The other chromosome 22 found in each of their somatic cells is normal. Some of their egg or sperm cells contain the gene change or deletion in chromosome 22 and some contain a normal chromosome 22. In other cases the deletion has occurred spontaneously during conception or is only found in some of the egg or sperm cells of either parent but not found in the other cells of their body.

Parents who have had a child with an autosomal dominant form of Opitz syndrome may or may not be at increased risk for having other affected children. If one of the parents is diagnosed with Opitz syndrome then each of their children has a 50% chance of inheriting the condition. If neither parent has symptoms of Opitz syndrome nor possesses a deletion, then it becomes more difficult to assess their chances of having other affected children.

In many cases they would not be at increased risk since the gene alteration occurred spontaneously in the embryo during conception. It is possible, however, that one of the parents is a carrier, meaning they possess a

change in the autosomal dominant Opitz gene but do not have any obvious symptoms. This parent's children would each have a 50% chance of inheriting the Opitz gene.

X-linked Opitz syndrome

Some people with the X-linked form of Opitz syndrome have a change (mutation) in a gene found on the X chromosome called the MID1 (midline1) gene. Changes in another X-linked gene called the MID2 gene may also cause Opitz syndrome in some cases. It is believed that the MID genes produce proteins involved in the development of midline organs. Changes in the MID gene prevent the production of enough normal protein for normal organ development.

The X-linked form of Opitz syndrome is inherited differently by men and woman. A woman with an X-linked form of Opitz syndrome has typically inherited a changed MID gene from her mother and a changed MID gene from her father. This occurs very infrequently. All of this woman's sons will have Opitz syndrome and all of her daughters will be carriers for Opitz syndrome. Only women can be carriers for Opitz syndrome since carriers possess one changed MID gene and one unchanged MID gene. Most carriers for the X-linked form of Opitz syndrome do not have symptoms since one normal MID gene is usually sufficient to promote normal development. Some carriers do have symptoms but they tend to be very mild. Daughters of carriers for Opitz syndrome have a 50% chance of being carriers and sons have a 50% chance of being affected with Opitz syndrome. A man with an X-linked form of Opitz syndrome will have normal sons but all of his daughters will be carriers.

Demographics

Opitz syndrome is a rare disorder that appears to affect all ethnic groups. The frequency of this disorder is unknown since people with this disorder exhibit a wide range of symptoms, making it difficult to diagnose and many possess mild or non-detectable symptoms.

Signs and symptoms

People with Opitz syndrome exhibit a wide range of medical problems and in some cases may not exhibit any detectable symptoms. This may be due in part to the genetic heterogeneity of this condition. Even people with Opitz syndrome who are from the same family can have different problems. This may mean there are other genetic and non-genetic factors that influence the development of symptoms in individuals who have inherited a changed or deleted Opitz gene. Most individuals with Opitz syndrome only have a few symptoms of the disorder such as wide set eyes and a broad prominent forehead. Opitz syndrome can, however, affect many of the organs and structures of the body and primarily affects the development of midline organs. The most common symptoms are: hypertelorism (wide-spaced eyes), broad prominent forehead, heart defects, hypospadias (urinary opening of the penis present on the underside of the penis instead of its normal location at the tip), undescended testicles, an abnormality of the anal opening, agenesis of the corpus callosum (absence of the tissue which connects the two sides of the brain), cleft lip, and clefts and abnormalities of the pharynx (throat) and larynx (voice-box), trachea(wind-pipe) and esophagus.

People with Opitz syndrome usually have a distinctive look to the face such as a broad prominent forehead, cleft lip, wide set eyes that may be crossed, wide noses with upturned nostrils, small chins or jaws, malformed ears, crowded, absent or misplaced teeth and hair that may form a 'widow's peak'. In many cases the head may appear large or small and out of proportion to the rest of the body.

Often people with Opitz syndrome have difficulties swallowing because of abnormalities in the pharynx, larynx, trachea, or esophagus. This can sometimes result in food entering the trachea instead of the esophagus, which can cause damage to the lungs and pneumonia, and can sometimes be fatal in small infants. Abnormalities in the trachea can sometimes make breathing difficult and may result in a hoarse or weak voice and wheezing.

Both males and females may have abnormal genitals and abnormalities in the anal opening. Males can have hypospadias and undescended testicles and girls may have minor malformation of their external genitalia. Heart defects are also often present and abnormalities of the kidney can be present as well. Intelligence is usually normal but mild mental retardation can sometimes be present. Twins appear more common in families affected with Opitz syndrome.

Males and females with the dominant form of Opitz syndrome are equally likely to have symptoms whereas carrier females with the X-linked form of Opitz syndrome are less likely to have symptoms then males with the condition. In general, males with the X-linked form of Opitz syndrome tend to be more severely affected than females and males with the autosomal dominant form of Opitz syndrome. People with X-linked Opitz syndrome and dominant Opitz syndrome generally appear to exhibit the same range of symptoms. The only known exceptions are upturned nostrils and clefts at the back of throat, which appear to only occur in people with X-linked Opitz syndrome.

TABLE 1

Frequencies of common conditions associated with Opitz syndrome

Hypospadias	93%	LTE cleft/fistula	38%
Hypertelorism	91%	Cleft lip and palate	32%
Swallowing problems	81%	Strabismus	28%
Ear abnormalities	72%	Heart defects	27%
Developmental delay	43%	Imperforate anus	21%
Kidney anomalies	42%	Undescended testes	20%

Diagnosis

Diagnostic testing

The diagnosis and cause of Opitz syndrome is often difficult to establish. In most cases, Opitz syndrome is diagnosed through a clinical evaluation and not through a blood test. This means a genetic specialist (geneticist) has examined the patient and found enough symptoms of Opitz syndrome to make a diagnosis. Since not all patients have obvious symptoms or even any symptoms at all, this can be a difficult task. It can also be difficult to establish whether an individual has an X-linked form or an autosomal dominant form, and whether it has been inherited or occurred spontaneously. In many cases, the geneticist has to rely on physical examinations or pictures of multiple family members and a description of the family's medical history to establish the cause of Opitz syndrome. In some cases the cause cannot be established.

Sometimes a clinical diagnosis is confirmed through fluorescence in situ hybridization (FISH). FISH testing can detect whether a person has a deletion of the region of chromosome 22 that is associated with Opitz syndrome. Fluorescent (glowing) pieces of **DNA** containing the region that is deleted in Opitz syndrome are mixed with a sample of cells obtained from a blood sample. If there is a deletion in one of the chromosomes, the DNA will only stick to one chromosome and not the other and only one glowing section of a chromosome will be visible instead of two. Most patients with the autosomal dominant form of Opitz syndrome cannot be diagnosed through FISH testing since they possess a tiny change in the gene that cannot be detected with this procedure. As of 2001, researchers are still trying to discover the specific gene and gene changes that cause autosomal dominant Opitz syndrome.

FISH testing is unable to detect individuals with the X-linked form of Opitz syndrome. As of 2001, DNA testing for the X-linked form of Opitz disease is not available through clinical laboratories. Some research laboratories are looking for changes in the MID1 gene and the MID2 gene as part of their research and may occasionally confirm a clinical diagnosis of X-linked Opitz syndrome.

Prenatal testing

It is difficult to diagnose Opitz syndrome in a baby prior to its birth. Sometimes doctors and technicians (ultrasonographers) who specialize in performing ultrasound evaluations are able to see physical features of Opitz syndrome in the fetus. Some of the features they may look for in the ultrasound evaluation are heart defects, wide spacing between the eyes, clefts in the lip, hypospadias, and agenesis of the corpus callosum. It is very difficult, however, even for experts to diagnose or rule-out Opitz syndrome through an ultrasound evaluation.

Opitz syndrome can be definitively diagnosed in a baby prior to its birth if a MID gene change is detected in the mother or if a deletion in chromosome 22 is detected in the mother or father. Cells from the baby are obtained through an **amniocentesis** or chorionic villus sampling. These cells are analyzed for the particular MID gene change or chromosome 22 deletion found in one of the parents.

Treatment and management

As of 2001 there is no cure for Opitz syndrome and no treatment for the underlying condition. Management of the condition involves diagnosing and managing the symptoms. Clefts, heart defects, and genital abnormalities can often be repaired by surgery. Feeding difficulties can sometimes be managed using feeding tubes through the nose, stomach, or small intestine. Early recognition and intervention with special education may help individuals with mental retardation.

Prognosis

For most patients, the prognosis and quality of life of Opitz syndrome is good, with individuals typically living a normal lifespan. The prognosis, however, is very dependent on the type of organ abnormalities and the quality of medical care. Patients with severe heart defects and major abnormalities in the trachea and esophagus may have a poorer prognosis.

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March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Opitz G/BBB Family Network. PO Box 515, Grand Lake, CO 80447. opitznet@mac.com. <http://www.gle.egsd.k12.co.us/opitz/index.html>.

Smith-Lemli-Opitz Advocacy and Exchange (RSH/SLO). 2650 Valley Forge Dr., Boothwyn, PA 19061. (610) 485-9663. <http://members.aol.com/slo97/index.html>.

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Lisa Maria Andres, MS, CGC

Opitz-Frias syndrome *see* **Opitz syndrome**

Opitz-Kaveggia syndrome *see* **FG syndrome**

Oral-facial-digital syndrome

Definition

Oral-facial-digital (OFD) syndrome is a generic name for a variety of different **genetic disorders** that result in malformations of the mouth, teeth, jaw, facial bones, hands, and feet.

Description

Oral-facial-digital syndrome includes several different but possibly related genetic disorders. OFD syndromes are also referred to as digito-orofacial syndromes. As of 2001, there are nine different OFD syndromes, identified as OFD syndrome type I, type II, and so on. OFD syndromes are so named because they all cause changes in the oral structures, including the tongue, teeth, and jaw; the facial structures, including the head, eyes, and nose; and the digits (fingers and toes). OFD syndromes are also frequently associated with developmental delay.

The different OFD syndromes are distinguished from each other based on the specific physical symptoms and the mode of **inheritance**. There are many alternate names for OFD syndromes. A partial list of these is:

- OFD syndrome type I: Gorlin syndrome I, Gorlin-Psaume syndrome, Papillon-Leage syndrome;
- OFD syndrome type II: Mohr syndrome, Mohr-Claussen syndrome;
- OFD syndrome type III: Sugarman syndrome;
- OFD syndrome type IV: Baraitser-Burn syndrome;
- OFD syndrome type V: Thurston syndrome;
- OFD syndrome type VI: Juberg-Hayward syndrome, Varadi syndrome, Varadi-Papp syndrome;
- OFD syndrome type VII: Whelan syndrome.

Genetic profile

The mode of inheritance of OFD syndrome depends on the type of the syndrome. Type I is inherited as an X-linked dominant trait and is only found in females because it is fatal in males. X-linked means that the syndrome is carried on the female sex chromosome, while dominant means that only one parent has to pass on the **gene mutation** in order for the child to be affected with the syndrome.

OFD syndrome type VII is inherited either as an X-linked or autosomal dominant pattern of inheritance. Autosomal means that the syndrome is not carried on a sex chromosome.

OFD syndrome types II, III, IV, V, and VI are passed on through an autosomal recessive pattern of inheritance. Recessive means that both parents must carry the gene mutation in order for their child to have the disorder.

OFD syndrome types VIII and IX are characterized by either an autosomal or X-linked recessive pattern of inheritance.

The gene location for OFD syndrome type I has been assigned to Xp22.3-22.2, or, on the 22nd band of the p arm of the X chromosome. As of 2001, the specific gene

KEY TERMS

Digit—A finger or toe. Plural–digits.

mutations responsible for the other types of OFD syndrome have not been identified.

Demographics

There does not appear to be any clear-cut ethnic pattern to the incidence of OFD syndrome. Most types of OFD syndrome affect males and females with equal probability, although type I, the most common type, affects only females (since it is lethal in males before birth). The overall incidence of OFD syndrome has not been established due to the wide variation between the different types of the syndrome and the difficulty of definitive diagnosis.

Signs and symptoms

The symptoms observed in people affected by OFD syndrome vary depending on the specific type of the syndrome. In general, the symptoms include the following:

Oral features:

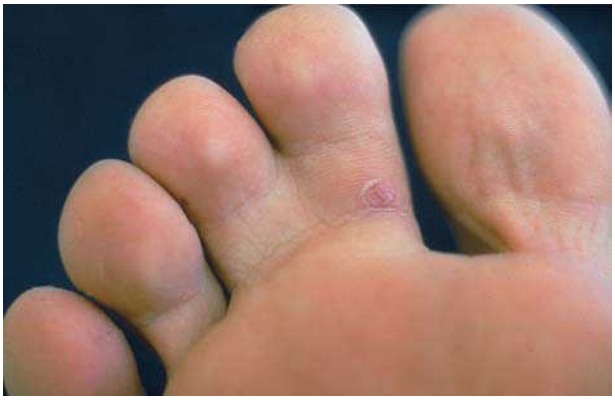
- Cleft lip
- Cleft palate or highly arched palate
- Lobed or split tongue
- Tumors of the tongue
- Missing or extra teeth
- Gum disease
- Misaligned bite
- Smaller than normal jaw

Facial features:

- Small or wide set eyes
- Missing structures of the eye
- Broad base or tip of the nose
- One nostril smaller than the other
- Low-set or angled ears

Digital features:

- Extra fingers or toes
- Abnormally short fingers
- Webbing between fingers or toes
- **Clubfoot**
- Permanently flexed fingers



One of the many traits found in individuals with OFD syndrome is webbing of the fingers and toes. *(Custom Medical Stock Photos, Inc.)*

Mental development and central nervous system:

- Mental retardation
- Brain abnormalities
- Seizures
- Spasmodic movements or tics
- Delayed motor and speech development

Other:

- Growth retardation
- Cardiovascular abnormalities
- Sunken chest
- Susceptibility to respiratory infection

Diagnosis

Diagnosis is usually made based on the observation of clinical symptoms. There is currently no medical test that can definitively confirm the diagnosis of OFD syndrome, with the exception of genetic screening for OFD syndrome type I.

Treatment and management

Treatment of OFD syndrome is directed towards the specific symptoms of each case. Surgical correction of the oral and facial malformations associated with OFD syndrome is often required.

Prognosis

Prognosis depends on the specific type of OFD syndrome and the symptoms present in the individual. OFD syndrome type I is lethal in males before birth. However, other types of OFD syndrome are found in both males and females. Due to the wide variety of symptoms seen

in the nine types of the syndrome, overall survival rates are not available.

Resources

ORGANIZATIONS

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

FACES: The National Craniofacial Association. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paul A. Johnson

Organic acidemias

Definition

Organic acidemias are a collection of amino and fatty acid oxidation disorders that cause non-amino organic acids to accumulate and be excreted in the urine.

Description

Organic acidemias are divided into two categories: disorders of amino acid metabolism and disorders involving fatty acid oxidation. There are several dozen different organic acidemia disorders. They are caused by inherited deficiencies in specific enzymes involved in the breakdown of branched-chain amino acids, lysine, and tryptophan, or fatty acids. Some have more than one cause.

Amino acids are chemical compounds from which proteins are made. There are about 40 amino acids in the human body. Proteins in the body are formed through various combinations of roughly half of these amino acids. The other 20 play different roles in metabolism. Organic acidemias involving amino acid metabolism disorders include isovaleric acidemia, 3-methylcrotonylglycemia, combined carboxylase deficiency, hydroxymethylglutaric acidemia, **propionic acidemia**, methylmalonic acidemia, beta-ketothiolase deficiency, and glutaric acidemia type I.

Fatty acids, part of a larger group of organic acids, are caused by the breakdown of fats and oils in the body. Organic acidemias caused by fatty acid oxidation disorders include, glutaric acidemia type II, short-chain acyl-CoA dehydrogenase (SCAD) deficiency, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, long-chain acyl-CoA dehrdrogenase (LCAD) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency.

Most organic acidemias are considered rare, occurring in less than one in 50,000 persons. However, MCAD occurs in about one in 23,000 births. Most of these disorders produce life-threatening illnesses that can occur in newborns, infants, children, and adults. In nearly all cases, though, the symptoms appear during the first few years of life, usually in children age two or younger. If left undiagnosed and untreated in young children, they can also delay physical development.

Genetic profile

Genes are the blueprint for the human body, directing the development of cells and tissue. Mutations in some genes can cause **genetic disorders** such as the organic acidemias. Every cell in the body has 23 pairs of **chromosomes**, 22 pairs of which contain two copies of individual genes. The twenty-third pair of chromosomes is called the sex chromosome because it determines a person's gender. Men have an X and a Y chromosome while women have two X chromosomes.

Organic acidemias are generally believed to be autosomal recessive disorders that affect males and females. Autosomal means that the **gene** does not reside on the twenty-third or sex chromosome. People with only one abnormal gene are carriers but since the gene is recessive, they do not have the disorder. Their children

will be carriers of the disorder 50% of the time but not show symptoms of the disease. Both parents must have one of the abnormal genes for a child to have symptoms of an organic acidemia. When both parents have the abnormal gene, there is a 25% chance each child will inherit both abnormal genes and have the disease. There is a 50% chance each child will inherit one abnormal gene and become a carrier of the disorder but not have the disease itself. There is a 25% chance each child will inherit neither abnormal gene and not have the disease nor be a carrier.

Demographics

Organic acidemias affect males and females roughly equally. The disorders primarily occur in Caucasian children of northern European ancestry, such as English, Irish, German, French, and Swedish. In a 1994 study by Duke University Medical Center, 120 subjects with MCAD were studied. Of these, 118 were Caucasian, one was black, and one was Native American; 65 were female and 55 were male; and 112 were from the United States while the other eight were from Great Britain, Canada, Australia, and Ireland.

Signs and symptoms

Symptoms of organic acidemias vary with type and sometimes even within a specific disorder. Isovaleric acidemia (IA) can present itself in two ways: acute severe or chronic intermittent. Roughly half of IA patients have the acute sever disorder and half the chronic intermittent type. In acute severe cases, patients are healthy at birth but show symptoms between one to 14 days later. These symptoms include vomiting, refusal to eat, dehydration, listlessness, and lethargy. Other symptoms can include shaking, twitching, convulsions, and low body temperature (under 97.8ºF or 36.6ºC), and a foul "sweaty feet" odor. If left untreated, the infant can lapse into a coma and die from severe ketoacidosis, hemorrhage, or infections. In the chronic intermittent type, symptoms usually occur within a year after birth and is usually preceded by upper respiratory infections or an increased consumption of protein-rich foods, such as meat and dairy products. Symptoms include vomiting, lethargy, "sweaty feet" odor, acidosis, and ketonuria. Additional symptoms may include diarrhea, thrombocytopenia, neutropenia, or pancytopenia.

There is a wide range of symptoms for 3-methylcrotonglycemia, which can occur in newborns, infants, and young children. These include irritability, drowsiness, unwillingness to eat, vomiting, and rapid breathing. Other symptoms can include hypoglycemia, alopecia, and involuntary body movements.

Approximately 30% of patients with hydroxymethylglutaric acidemia show symptoms within five days after birth and 60% between three and 24 months. Symptoms vary and can include vomiting, deficient muscle tone, lethargy, seizures, metabolic acidosis, hypoglycemia, and hyperammonemia.

Symptoms of methylmalonic acidemia (MA) due to methylmalonyl-CoA mutase (MCoAM) deficiency include lethargy, failure to thrive, vomiting, dehydration, trouble breathing, deficient muscle tone, and usually present themselves during infancy. MA due to N-methyltetrahydrofolate: homocysteine methyltransferase deficiency and high homocysteine levels usually occurs during the first two months after birth but has been reported in children as old as 14 years. General symptoms are the same as for MA due to MCoAM but can also include fatigue, delirium, **dementia**, spasms, and disorders of the spinal cord or bone marrow.

Symptoms of glutaric acidemia type I usually appear within two years after birth and generally become apparent when a minor infection is followed by deficient muscle tone, seizures, loss of head control, grimacing, and **dystonia** of the face, tongue, neck, back, arms, and hands. Glutaric acidemia type II symptoms fall into three categories:

- Infants with congenital anomalies present symptoms within the first 24 hours after birth, with symptoms of deficient muscle tone, severe hypoglycemia, hepatomegaly (enlarged liver), metabolic acidosis, and sometimes a "sweaty feet" odor. In some patients, signs include a high forehead, low-set ears, enlarged kidneys, excessive width between the eyes, a mid-face below normal size, and genital anomalies.
- Infants without congenital anomalies have signs of deficient muscle tone, tachypnea (increased breathing rate), metabolic acidosis, hepatomegaly, and a "sweaty feet" odor.
- Mild or later onset symptoms in children that include vomiting, hypoglycemia, hepatomegaly, and myopathy (a disorder of muscle or muscle tissue).

There are two types of propionic acidemia, one caused by propionyl-CoA carboxylase (PCoAC) deficiency and the other caused by multiple carboxylase (MC) deficiency. Symptoms of both disorders are generally the same and include vomiting, refusal to eat, lethargy, hypotonia, dehydration, and seizures. Other symptoms may include skin rash, ketoacidosis, irritability, metabolic acidosis, and a strong smelling urine commonly described as "tom cats'" urine.

There are five types of organic acidemias of fatty acid oxidation that involve deficiencies of acyl-CoA dehydrogenase enzymes: SCAD, MCAD, LCAD,

KEY TERMS

Acidosis—A condition of decreased alkalinity resulting from abnormally high acid levels (low pH) in the blood and tissues. Usually indicated by sickly sweet breath, headaches, nausea, vomiting, and visual impairments.

Alopecia—Loss of hair or baldness.

Biotin—A growth vitamin of the vitamin B complex found naturally in liver, egg yolks, and yeast.

Branched-chain—An open chain of atoms having one or more side chains.

Dystonia—Painful involuntary muscle cramps or spasms.

Homocysteine—An amino acid that is not used to produce proteins in the human body.

Hyperammonemia—An excess of ammonia in the blood.

Hypotonia—Reduced or diminished muscle tone.

Ketoacidosis—A condition that results when organic compounds (such as propionic acid, ketones, and fatty acids) build up in the blood and urine.

Ketolactic acidosis—The overproduction of ketones and lactic acid.

Ketonuria—The presence of excess ketone bodies (organic carbohydrate-related compounds) in the urine.

L-carnitine—A substance made in the body that carries wastes from the body's cells into the urine.

Lysine—A crystalline basic amino acid essential to nutrition.

Metabolic acidosis—High acidity (low pH) in the body due to abnormal metabolism, excessive acid intake, or retention in the kidneys.

Neutropenia—A condition in which the number of leukocytes (a type of white or colorless blood cell) is abnormally low, mainly in neutrophils (a type of blood cell).

Organic aciduria—The condition of having organic acid in the urine.

Pancytopenia—An abnormal reduction in the number of erythrocytes (red blood cells), leukocytes (a type of white or colorless blood cell), and blood platelets (a type of cell that aids in blood clotting) in the blood.

Thrombocytopenia—A persistent decrease in the number of blood platelets usually associated with hemorrhaging.

Tryptophan—A crystalline amino acid widely distributed in proteins and essential to human life.

VLCAD, and LCHAD. General symptoms for all five of these disorders include influenza- or cold-like symptoms, hyperammonemia, metabolic acidosis, hyperglycemia, vomiting, a "sweaty feet" odor, and delay in physical development. In young children, other symptoms can include loss of hair, involuntary or uncoordinated muscle movements (ataxia), and a scaly rash (seborrhea rash.) Symptoms generally appear between two months and two years of age, but can appear as early as two days after birth up to six years of age.

There are two combined carboxylase deficiency organic acidemias: holocarboxylase synthetase deficiency and biotindase deficiency. Symptoms of holocarboxylase deficiency include sleep and breathing difficulties, hypotonia, seizures, alopecia, developmental delay, skin rash, metabolic acidosis, ketolactic acidosis, organic aciduria, and hyperammonemia. Symptoms of biotindase deficiency include seizures, involuntary muscular movements, hypotonia, rapid breathing, developmental delay, hearing loss, and visual problems. Skin rash, alopecia, metabolic acidosis, organic acidemia, and hyper ammonemia can also occur.

Symptoms of beta-ketothiolase deficiency vary. In infants, the most common symptoms include severe metabolic acidosis, ketosis, vomiting, diarrhea (often bloody), and upper respiratory or gastrointestinal infections. Adults with the disorder are usually asymptomatic (showing no outward signs of the disease).

Diagnosis

In all types of organic acidemia, diagnosis cannot be made by simply recognizing the outward appearance of symptoms. Instead, diagnosis is usually made by detecting abnormal levels of organic acid cells in the urine through a urinalysis. The specific test used is called combined gas chromatography-mass spectrometry. In gas chromatography, a sample is vaporized and its components separated and identified. Mass spectrometry electronically weighs molecules. Every molecule has a unique weight (or mass). In newborn screening, mass spectrometry analyzes blood to identify what amino acids and fatty acids are present and the amount present.

The results can identify if the person tested has a specific organic acidemia. Many organic acidemias also can be diagnosed in the uterus by using an enzyme assay of cultured cells, or by demonstrating abnormal organic acids in the fluid surrounding the fetus. In some laboratories, analysis is done on blood, skin, liver, or muscle tissue. Molecular DNA testing is also available for common mutations of MCAD and LCHAD.

Since most organic acidemias are rare, routine screening of fetuses or newborns is not usually done and are not widely available. In MCAD, a more common organic acidemia, abnormal organic acids are excreted in the urine intermittently so a diagnosis is made by detecting the compound phenylpropionylglycine in the urine.

Treatment and management

There are few medications available to treat organic acidemias. The primary treatments are dietary restrictions tailored to each disorder, primarily restrictions on the intake of certain amino acids. For example, patients with some acidemias, such as isovaleric and beta-ketothiolase deficiency, must restrict their intake of leucine by cutting back on foods high in protein. Patients with propionic or methylmalonic acidemias must restrict their intake of threonine, valine, methionine, and isoleucine. The intake of the restricted amino acids is based on the percentage of lean body mass rather than body weight. Some patients also benefit from growth hormones. Patients with combined carboxylase deficiency are sometimes treated with large doses of biotin. Some patients with methylmalonic acidemia are treated with large doses of vitamin B_{12}.

Glucose infusion (to provide calories and reduce the destructive metabolism of proteins) and bicarbonate infusion (to control acidosis) are often used to treat acute episodes of some acidemias, including isovaleric, 3-methylcrotonylglycemia, and hydroxymethylglutaric.

The primary treatment for MCAD is to not go without food for more than 10 or 12 hours. Children should eat foods high in carbohydrates, such as pasta, rice, cereal, and non-diet drinks, when they are ill. A low fat diet is also recommended. The drug L-carnitine is sometimes used by physicians to prevent low blood sugar when patients have infections or are not eating regularly.

The treatment of LCHAD is similar to that of MCAD, except that L-carnitine is usually not prescribed. Children with LCHAD are often treated with medium chain triglycerides oil.

Holocarboxylase synthetase deficiency is generally treated by administering 10 milligrams (mg) of biotin daily. Eating large amounts of yeast, liver, and egg yolks, which naturally contain biotin, did not improve the condition. **Biotinidase deficiency** is usually treated successfully with pharmacological doses of between five and 20 mg of biotin daily. However, hearing and vision problems appear to be less reversible.

Prognosis

The prognosis of patients with organic acidemias varies with each disorder and usually depends on how quickly and accurately the condition is diagnosed and treated. Some patients with organic acidemias are incorrectly diagnosed with other conditions, such as sudden infant death syndrome (SIDS) or Reye syndrome. Without a quick and accurate diagnosis, the survival rate decreases with each episode of the disorder. Death occurs within the first few years of life, often within the first few months. With a quick diagnosis and aggressive monitoring and treatment, patients can often live relatively normal lives. For example, children with either biotinidase deficiency or holocarboxylase synthetase deficiency, when detected early and treated with biotin, have generally shown resolution of the clinical symptoms and biochemical abnormalities.

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ORGANIZATIONS

Fatty Oxidation Disorders (FOD) Family Support Group. 805 Montrose Dr., Greensboro, NC 27410. (336) 547-8682. fodgroup@aol.com. <http://www.fodsupport.org/welcome.htm>.

National Newborn Screening and Genetics Resource Center. 1912 W. Anderson Lane, Suite 210, Austin, TX 78757. Fax: (512) 454-6419. <http://www.genes-r-us.uthscsa.edu>.

Organic Acidemia Association. 13210 35th Ave. North, Plymouth, MN 55441. (763) 559-1797. Fax: (863) 694-0017. <http://www.oaanews.org>.

Ken R. Wells

Ornithine transcarbamylase deficiency

Definition

Ornithine transcarbamylase deficiency is a disorder in which there is a failure of the body to properly process ammonia, which can lead to coma and death if left untreated.

Description

Persons with ornithine transcarbamylase deficiency (OTC deficiency) have a problem with nitrogen metabolism. Too much nitrogen in the blood in the form of ammonia can cause brain damage, coma, and death. Ammonia is made up of nitrogen and hydrogen. Ammonia found in humans mostly comes from the breakdown of protein, either protein broken down from muscles, organs, and tissues already in the body, or excess protein that is eaten in the diet. Since excess ammonia is harmful, it is immediately excreted in normal humans after passing through the urea cycle and becoming urea. Ornithine transcarbamylase is a **gene** involved in the urea cycle–the process of making ammonia into urea, which occurs in the liver.

It is important to make urea, because, unlike ammonia, urea an be excreted by the kidney into the urine. Ammonia, on the other hand, cannot be effectively excreted by the kidney. So, if the ornithine transcarbamylase (OTC) function is reduced or impaired, ammonia builds up in the bloodstream. This buildup of ammonia in the bloodstream can lead to consequences as severe as coma and death. The amount of ammonia found in the bloodstream, and the severity of the disorder, depend on how well the OTC gene functions. If it functions reasonably well, the person should have a minor form of the disorder or no disorder. If the gene functions extremely poorly, or not at all, the disorder will be severe.

Synonyms for ornithine transcarbamylase deficiency include Hyperammonemia Type II, Ornithine carbamyl transferase deficiency, OTC deficiency, UCE, **Urea cycle disorder**, OTC Type, and Hyperammonemia due to ornithine transcarbamylase deficiency.

Genetic profile

OTC deficiency is an X-linked recessive disorder. This means that it is found on the X chromosome (specifically, it is located on the short arm at Xp21.1) Recessive disorders require that only abnormal genes, and no normal genes, be present. For non-sex **chromosomes**, this means that both copies of a gene (one received from each parent) must be abnormal in order for that person to have the disorder.

In X-linked recessive disorders, however, only one abnormal copy of a gene must be present to cause the disorder in males. Males possess only one X chromosome, from thier mother, and one Y chromosome, which they receive from their father. If the mother is a carrier for the disorder (she has one normal gene and one abnormal gene), a male child would have a 50% chance of receiving an abnormal gene from her. If he receives the abnormal gene, he will have the disorder. So male children of a female carrier have a 50% chance of having the disorder.

A female child of a female carrier is much less likely to have the disorder. Unless the father has OTC deficiency, a female child will have one normal and one abnormal gene. Since recessive disorders require that both genes be mutated, the female child cannot have the disorder. Females with only one mutant OTC gene may have a mild form of the disorder because it is not purely recessive. Usually, the normal copy of the gene can sufficiently compensate for the poor functioning of the second, abnormal gene.

Some females do have the full-blown disorder, probably because of a phenomenon called X-inactivation. Although females have two X chromosomes in each cell, only one is active. Therefore, it is possible a female could have the disorder because only the abnormal gene was active in each cell of the liver, which is where OTC function takes place. Not enough is known about X-inactivation to speculate on the likelihood of this occuring. Overall, many more men than women have the disease. This means that OTC disease due to X-inactivation is not very common.

If the father has the gene for the disorder, he cannot pass it on to his male child (he does not give the male child an X chromosome, only a Y). He can give his female child one copy of the gene, which might result in a mild form of the disorder or the full-blown disorder due to X-inactivation.

Demographics

OTC affects infants at the rate of approximately one birth in every 70,000. As expected with an X-linked disorder, the disorder is more common in males.

Signs and symptoms

Before birth there are no symptoms of OTC deficiency because the exchange of nutrients and fluids between the mother and fetus allows the excess ammonia to leave the infant's blood and go into the mother's blood. The mother is then able to get rid of the ammonia as urea because she either lacks the disorder or her ammonia levels are medically well-controlled.

The most severe cases of OTC deficiency usually present in infants before they are a week old, typically in males. It may take several days for symptoms to appear, since it takes that long for protein, and therefore ammonia levels, to build up in the infant. Affected infants generally show periods of inactivity, a failure to feed, and vomiting. Unfortunately, many other disorders may also present with these same general symptoms, and new parents may not recognize these as abnormal in an infant. These symptoms are always accompanied in OTC deficiency by hyperammonemia, or high levels of ammonia in the blood.

Hyperammonemia is the most important symptom for identification and treatment of ornithine transcarbamylase deficiency. It is the cause of all other symptoms seen in OTC deficiency. Additionally, hepatomegaly (an enlarged liver), and seizures may also be present. If the disorder, or at least the hyperammonemia, is not recognized and treated, the symptoms may progress into coma and eventually, death. A failure to quickly resolve the hyperammonemia once an infant lapses into a coma may also lead to severe mental retardation or death.

Patients with milder forms of the disorder may show symptoms later in life such as failure to grow at a normal rate or they may experience developmental delay. Developmental delay is an inability to reach recognized milestones like speaking or grasping objects at an appropriate age. These milder symptoms would be accompanied by hyperammonemia, but the levels of ammonia would be much lower than in an episodic attack of hyperammonemia or in the severely ill infant. Other persons with mild forms of the disorder may have no symptoms, or may only experience nausea after a meal with a large protein content.

Persons with a mild form of the disorder and no other symptoms may also learn they have the disorder from an episode of acute hyperammonemia. Acute conditions are brief and immediate, whereas chronic conditions are long-lasting.

An episodic attack of acute hypperammonemia, then, is a an episode where levels of ammonia climb above what may be already high levels of ammonia. A person with an episode of acute hyperammonemia can have symptoms including some, or all, of the following: vomiting, lack of apetite, drowsiness, hepatomegaly, seizures, coma, and death. These episodes can be life-threatening and may require hospitalization depending on their severity and response to medication.

These episodic attacks are probably related to a large increase in the amount of protein being broken down in the body, which results in too much ammonia being produced. This ammonia cannot be immediately excreted, which results in hyperammonemia. The most common reasons for a change in the amount of protein broken down are probably starvation, illness, and surgery. Even persons with no previous symptoms can experience a fatal episode of acute hyperammonemia brought on by an increase in protein breakdown. Since an episodic attack of hyperammonemia can be fatal without any previous symptoms, persons who have at least one family member with OTC deficiency should consider testing to determine whether they have the gene for the disorder. If the disorder is known to be present, an episode of hyperammonemia might be anticipated and its effect lessened.

Diagnosis

A definitive diagnosis of OTC deficiency is made by laboratory tests, since physical synptoms are very general and common to a large number of disorders. A high level of ammonia in the blood is the hallmark of this disorder and other disorders that affect the urea cycle. In the short term, the levels of two amino acids in the urine, orotate and citrulline, should distinguish between OTC deficiency and other urea cycle deficiencies. In OTC deficiency, citrulline levels are normal or low, and orotate levels are usually high. In the long term, however, the most definitive diagnosis can be made through **DNA** analysis, or through a test of OTC activity in a small piece of liver tissue (a biopsy) taken from the patient.

Prenatal diagnosis of the disorder is difficult and not indicated unless there is an affected family member with the disorder. In that case, if the mutation is known, DNA analysis would reveal the same mutation as in the family member with OTC deficiency. If the mutation is not known, a method called linkage analysis may be used. In linkage analysis, the OTC gene itself is not analyzed, but the DNA near the gene is analyzed. The "near DNA" can then be compared to the "near DNA" of the affected family member. If the DNAs are different, then the fetus should not have the disorder. If they are the same, then the fetus probably has the disorder.

Treatment and management

Long-term management

The severity of the disorder is the most important factor in determining long-term treatment of OTC deficiency. The most severely affected individuals, usually infant males, should have liver transplants. As previously mentioned, the urea cycle and OTCs function occur in the liver. The transplantation immediately corrects OTC deficiency. Episodes of life-threatening ammonemia are prevented, although monitoring of tissue levels of ammonia is suggested. Another important benefit is that the transplant allows the child to develop and grow in a normal manner, without the threat of developmental delay or mental retardation. Transplants are now recommended even for children less than one year of age with a severe form of the disorder.

Two problems with liver transplants exist, however. First, it is difficult to obtain a liver from among the limited supply of donors, especially if the child is not currently hospitalized. The second problem arises from the way in which organs are assigned. Persons who are critically ill receive priority in organ donor lists. This means children whose disease is manageable may not be able to receive a transplant.

Second, children with transplants must have their immune system suppressed. The immune system fights off, and lets one recover from infections like colds, flus, and chicken pox. However, it also fights the introduction of an organ from someone else's body, even a relative—except identical twins. Thus, as long as a person has a transplant, that person must have their immune system suppressed so that the transplanted organ is not killed by the body it is in. The problem with immune suppression is that a person is much more likely to become sick. This disadvantage is far outweighed by the advantages of normal mental development and the prevention of death in patients with severe OTC deficiency.

Patients in rural areas, or areas where there is no immediate access to a hospital equipped to care for a patient with an acute attack of hyperammonemia, should also be strongly considered for a liver transplant if the patient is predisposed to attacks of life-threatening hyperammonemia.

For less severely affected children, or children unable to obtain a liver transplant, long-term therapy consists of a combination of drugs, usually oral, sodium phenylbutyrate, and diet. This bypasses the normal process of the breakdown of protein into urea in the liver, which is the usual way that ammonia leaves the body. Children with OTC deficiency are placed on a low protein diet so their protein breakdown system does not become overwhelmed and lead to hyperammonemia. Children with OTC deficiency are also given arginine, an amino acid, which, for reasons that are unclear, causes more nitrogen, which is part of ammonia, to be excreted in the urine, and lowers blood ammonia. Dietary regimens vary from patient to patient based on their age, size, and the severity of the disorder. A nutrition expert must be consulted when developing an appropriate diet. The most strict diet consists of vitamin supplements and no protein other than essential amino acids. Essential amino acids are those that cannot be made by the body and must be obtained through food. Since proteins are made up of amino acids, and only amino acids, that means this diet is extremely restrictive. It also means that very little ammonia is left in the bloodstream since most of the otherwise free ammonia is tied up in the synthesis of the non-essential amino acids, amino acids made by the body itself.

Any chronic disease is stressful for a family. Parents and patients should consider support and information groups like the National Urea Cycle Disorders Foundation.

Short-term management

Short-term management of attacks of crisis hyperammonemia (severe acute hyperammonemia) consists of dialysis and drug therapy. Dialysis and large doses of the drugs sodium benzoate and sodium phenylacetate and doses of arginine are used to decrease the levels of ammonia in the blood. These methods are used together due to their synergistic effect.

Dialysis is a process where a toxic substance is removed from the blood. This can best be understood by pouring a small amount of cola into a glass. Now pour a large amount of water into it. In this way, the cola is "watered down" or diluted. Ammonia is diluted in a similar way using dialysis. Blood is removed from a patient and run through a hose. At one point, this hose runs through a tank made up of liquid that contains all

KEY TERMS

Developmental delay—When children do not reach certain milestones at appropriate ages. For example, a child should be able to speak by the time he or she is five years old.

Hyperammonemia—An excess of ammonia in the blood.

Urea—A nitrogen-containing compound that can be excreted through the kidney.

Urea cycle—A series of complex biochemical reactions that remove nitrogen from the blood so ammonia does not accumulate.

the components of blood, but no ammonia (this liquid is like the water in the water and cola example). Thus, ammonia spreads throughout the blood and the liquid surrounding the hose (the same way cola will spread out throughout water added to the glass) and the amount of ammonia in the blood is reduced. By continuously pumping blood through the hose and changing the liquid around the hose, most of the ammonia can be removed from the blood. All of the really large particles, like red blood cells, are also kept in the blood because the hose has holes that are only large enough to let smaller particles like ammonia out while keeping red blood cells in.

The future

The future treatment of OTC deficiency probably will come from experiments in **gene therapy**. OTC deficiency is a disorder particularly amenable to gene therapy because only one gene is affected and only one organ, the liver, would need the new gene. However, as of 2001, gene therapy has not been successfully demonstrated in human beings. Many technical problems must still be solved in order to successfully treat OTC deficiency and other disorders like it with gene therapy.

Prognosis

Only 50% of the most severely affected patients live beyond the time they first attend school. Of those receiving liver transplants, 82% of patients survive five years after receiving the transplant. Children with the severe disorder that receive drug therapy are much more likely to experience mental retardation, developmental delay, and a lack of growth. Also, many infants who experience hyperammonemic comas have severe mental damage.

For individuals not identified at birth or soon after, the prognosis varies widely. The consequences of the disorder are affected by the severity of the disorder and how it is managed, although anyone with the disorder may experience life-threatening attacks of acute hyperammonemia. In terms of long-term survival, puberty appears to be a difficult time for those with OTC deficiency, and persons who survive until after puberty have improved outcomes. The prognosis for this disorder can vary from quite hopeful to very distressing based upon its severity and how well the disorder can be controlled. A severe disorder that is well-controlled may still have a positive outcome.

Resources

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ORGANIZATIONS

National Urea Cycle Disorders Foundation. 4841 Hill Street, La Canada, CA 91011. (800) 38NUCDF. <http://www.NUCDF.org/>.

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“Ornithine transcarbamylase deficiency.” *NORD—National Organization for Rare Diseases.* <http://www.rarediseases.org>.

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Michael V. Zuck, Ph D

Osler-Weber-Rendu syndrome

Definition

Osler-Weber-Rendu syndrome (OWR), or hereditary hemorrhagic telangiectasia (HHT), is a blood vessel disorder, typically involving recurrent nosebleeds and telangiectases (arteriovenous malformations that result in small red spots on the skin) of the lips, mouth, fingers, and nose. Arteriovenous malformations (AVMs) are abnormal, direct connections between the arteries and veins (blood vessels), causing improper blood flow. AVMs are often present in OWR, and may occur in the lungs, stomach, or brain.

Description

The story of OWR began years ago with a sequence of events between three prominent physicians, Osler, Weber, and Rendu. The earliest report of OWR was compiled by Rendu in 1896. Osler further characterized the condition in 1901, and F. Parkes Weber described many cases of the vascular problems as well. OWR is caused by a genetic defect in the development of blood capillaries. Capillaries are vessels that exist between arteries and veins, connecting them throughout the body. The abnormality causes the capillaries to end bluntly, so they cannot properly connect the arteries and veins. Because of this, AVMs and telangiectases may result in various parts of the body.

Telangiectases on the skin represent a small AVM that has reached the outer surface of skin. Telangiectases usually have thin walls and are quite fragile, so they may burst spontaneously, causing bleeding. This bleeding may occur in the nose, explaining the frequent nosebleeds that result from little trauma. Telangiectases most often occur on the cheeks, lips, tongue, fingers, mouth,

and toes. Occasionally, larger AVMs may exist in the brain, lungs, or stomach and this may lead to more serious bleeding. It is very rare for an individual to have all the symptoms typically found in OWR.

People with OWR do not have any mental limitations, and therefore have the same academic potential as anyone else. Nosebleeds may begin by age twelve, and may be initially assumed to be a typical childhood experience. However, if fatigue and other symptoms of anemia accompany the nosebleeds, they can pose great stress on a young child. Children with OWR may find it difficult if they play with and are unable to keep up with their peers. OWR has the potential need for continual medical management into adulthood, which can also be quite taxing on the individual and his or her family.

Genetic profile

OWR may be divided into two groups, OWR1 and OWR2. OWR1 is caused by alterations in the endoglin (ENG) **gene**, located on the q (long) arm of chromosome 9 at band (location) 34. AVMs of the lung may be more common in OWR1 than OWR2. OWR2 is caused by alterations in the activin receptor-like kinase 1 gene (ALK1), located on the q arm of chromosome 12 at band 1. Normally, ENG and ALK1 make proteins that are important in blood vessel formation. Therefore, alterations within these genes would naturally cause problems with blood vessels. The causes of OWR are complex; various alterations in multiple genes, or various alterations within the same gene, generate similar symptoms.

OWR is inherited in an autosomal dominant manner. An affected individual has one copy of an alteration that causes OWR. The individual has a 50% chance to pass the alteration on to each of his or her children, regardless of that child's gender. As of 2000, nearly all affected people have a family history of OWR, which is typically a parent with the condition.

Demographics

As of 2000, OWR affects about one in 10,000 people. It spans the globe, but a higher prevalence exists in the Danish island of Fyn, the Dutch Antilles, and parts of France. It affects both males and females.

Signs and symptoms

The symptoms in OWR result from several AVMs, which may occur in differing severity and areas of the body. Ultimately, AVMs may lead to mild or severe bleeding in affected areas. As of 1998, about 90% of people with OWR experience frequent nosebleeds. They occur because the layers of mucous membranes in the nose are very sensitive and fragile, and AVMs in this area can easily and spontaneously bleed. Consistent nosebleeds may begin by about twelve years of age, and are not always severe enough to result in medical treatment or consultation. Occasionally, severe nosebleeds can cause mild to severe anemia, sometimes requiring a blood transfusion or iron replacement therapy.

Small AVMs, called telangiectases, commonly occur on the nose, lips, tongue, mouth, and fingers. They may vary in size from a pinpoint to a small pea. Because telangiectases are fragile, sudden bleeding may occur from only slight trauma, and bleeding may not sponta-

KEY TERMS

Alteration—Change or mutation in a gene, specifically in the DNA that codes for the gene.

Aneurysm—Widening of an artery, which could eventually bleed.

Arteriovenous malformation (AVM)—Abnormal, direct connection between the arteries and veins (blood vessels). Can range from very small to large in size. Bleeding or an aneurysm may result.

Cauterization—Process of burning tissue either with a laser or electric needle to stop bleeding or destroy damaged tissue.

Echocardiogram—A non-invasive technique, using ultrasonic waves, used to look at the various structures and function of the heart.

Embolization therapy—Introduction of various substances into the circulation to plug up blood vessels in order to stop bleeding.

Endoscopy—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Stroke—A sudden neurological condition related to a block of blood flow in part of the brain, which can lead to a variety of problems, including paralysis, difficulty speaking, difficulty understanding others, or problems with balance.

Telangiectasis—Very small arteriovenous malformations, or connections between the arteries and veins. The result is small red spots on the skin known as "spider veins".

neously stop. Thirty percent of people with OWR report telangiectases first appearing before age 20, and 67% before age 40. Telangiectases and larger AVMs can be found anywhere in the gastrointestinal system, and if large enough they may cause a significant amount of internal bleeding. This bleeding may become more severe with age, but usually does not appear until age forty.

Pulmonary AVMs (AVMs of the lung) may cause bleeding within the lungs. As of 1998, this occurs in about 20% of people with OWR. These are problematic because the abnormal connections between arteries and veins bypass the natural filtering system within the lung, allowing bacteria to enter the system. Low levels of oxygen and infection may result, causing migraine-like headaches. An individual with a pulmonary AVM may experience intolerance to exercise, or may have areas of their skin turn blue (due to low oxygen levels). Complications in the brain may also result, sometimes causing a stroke. Occasionally, AVMs may occur in the spine, liver, and brain. A network of AVMs in the liver can cause blood to be forced away from the normal circulation, increasing the risk of heart failure because the heart becomes overloaded with blood.

Diagnosis

As of 2001, **genetic testing** is available for OWR, but only on a research basis. The University of Utah offers linkage analysis to determine alterations in either ENG or ALK1, and results are not guaranteed. Linkage analysis is a method of genetic testing that requires several family members, both affected and unaffected, to give a blood sample for **DNA** analysis. The testing attempts to study family markers on the various **chromosomes**, in an attempt to find alterations near the proposed gene location. Results are abnormal if an alteration near ENG or ALK1 is found. If a familial alteration is identified, unaffected individuals could be offered testing to see whether or not they have the same alteration. If an individual had the alteration, he or she would be at risk for symptoms of OWR. Currently, no prenatal testing is available for OWR.

Because testing is neither widely available nor useful for diagnostic purposes, most people with OWR are identified by careful physical examination and study of their medical and family histories. Findings suggestive of an OWR diagnosis include nosebleeds (especially at night), multiple telangiectases (especially on the lips, mouth, fingers, and nose), and AVMs of various organs (especially the lungs, brain, liver, spine, and gastrointestinal (GI) tract). The final piece is a family history of OWR, with the affected person having the mentioned symptoms. OWR is considered definite when three or more findings are present, possible/suspected when two findings are present, and unlikely when fewer than two findings are present.

OWR is difficult to diagnose (and often under-diagnosed) because bleeding and venous malformations happen in otherwise healthy individuals. For example, isolated nosebleeds are very common in the general population and may occur for a variety of reasons. Because nosebleeds are often the first sign in OWR, they may initially be ignored, until they become so frequent that they are brought to medical attention. Isolated internal bleeding, or aneurysms, are quite common in the brain and GI tract. However, not all aneurysms are caused by AVMs and this needs to be determined, as AVMs are more specific to OWR. Most individuals with a pulmonary AVM actually have OWR.

Telangiectases may sometimes be a sign of other bleeding disorders, such as **von Willebrand disease**, a problem with blood coagulation (clotting). Telangiectases may also naturally occur in pregnancy or chronic liver disease. A hereditary form of telangiectases exists, and in this they are usually found on the face, upper limbs, and upper trunk of the body. Ataxia telangiectasia, another genetic condition involving telangiectases, should be considered if individuals have ataxia (problems with muscle coordination); movement and walking disorders are often observed with this condition as well.

Treatment and management

Treatment for OWR is based on the specific symptoms an individual experiences. To assess the need for treatment, a review of medical history regarding nosebleeds and other bleeding episodes should be noted. There should be careful inspection of any telangiectases. Stool samples may be analyzed to determine whether there is any blood present that is not obvious to the naked eye; this may indicate anemia. A complete blood count (CBC) can also determine whether anemia is a factor, due to blood loss. Pulse oximetry involves studying a blood sample, and determining whether the amount of oxygen absorption by red blood cells is normal. It can help to determine whether the lungs and heart are functioning properly, because their roles are to help oxygenate blood. Careful imaging of the heart by echocardiogram or chest x rays can assess whether the heart structures are normal. Chest x rays may identify pulmonary AVMs. Magnetic resonance imaging (MRI) of the head can visualize the brain to rule out any bleeding. An ultrasound of the liver and abdomen can help to rule out any AVMs in this area.

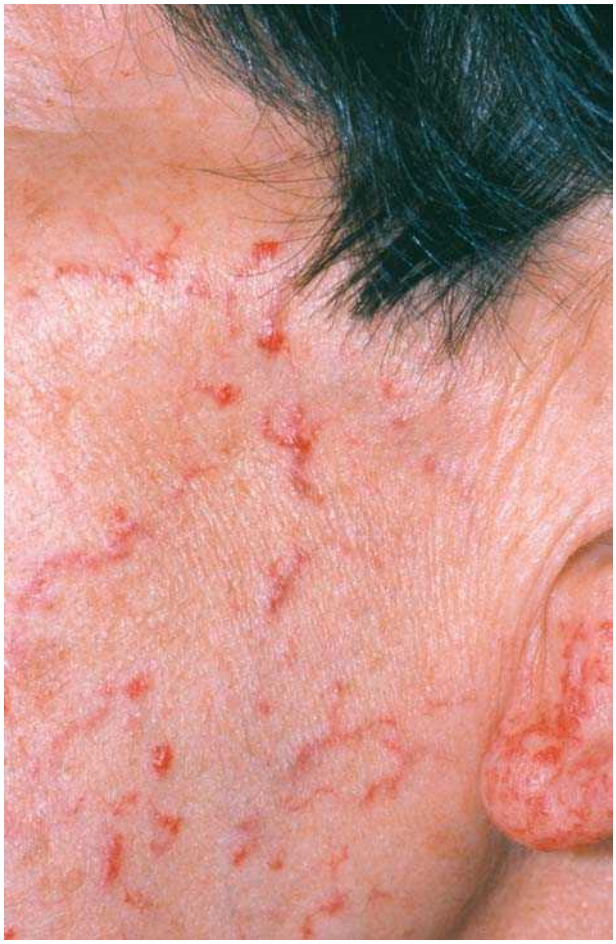
There are a few options for those who experience chronic nosebleeds. Generally, sterile sponges and sprays

may help absorb free-flowing blood. Another option is laser therapy, used for individuals who have mild to moderate nosebleeds. A small laser beam is directed around each telangiectasis, and automatic clotting occurs, sealing them. It is usually done under local anesthesia, and few complications exist. Nearly everyone sees improvements for several months, and the procedure may be repeated as needed. For more severe cases (sometimes requiring transfusions) there is septal dermoplasty, first pioneered in the 1960s. This replaces the normally fragile lining of the nose with a tougher lining, using a skin graft from the thigh area. The procedure can be done with local or general anesthetic, and has minimal complications. Some individuals never have nosebleeds again after the operation, but most of them experience a significant lessening of symptoms. Estrogen and aminocaproic acid (an amino acid) therapies have also been found to help with clotting in the nose. Estrogen improves the smoothness of layers of skin on the telangiectases, making them less fragile. Aminocaproic acid improves the clotting process by magnifying the protein responsible for clotting.

Gastrointestinal bleeding is one of the most difficult symptoms of OWR to treat. Endoscopy can help to identify the location of the AVM. Using an endoscopic probe, treatment can be attempted by laser or through cauterization—sealing the injury with heat. These help to seal the telangiectasis or AVM. If bleeding is severe, iron therapy is often needed to help build more red blood cells and alleviate anemia. Hormone therapy (with estrogen and progesterone) has been helpful in many patients with chronic GI bleeding. As of 1998, no perfect treatment for liver AVMs has been established, but embolization therapy has been used. For more severe cases (usually in older individuals) liver transplant may be considered.

Pulmonary AVMs are often treated with a procedure known as balloon embolization. A small tube is inserted into a large vein in the groin. It is passed through the blood vessels to the pulmonary AVM. A balloon or coil is placed into the artery leading into the AVM, blocking it off completely, and this stops the bleeding. This usually takes 1–2 hours, with minimal recuperation time. Pulmonary AVMs can almost always be treated very well with this method. Women with OWR who become pregnant and have untreated pulmonary AVMs run a high risk for an internal lung bleed. They should be treated during their second trimester to avoid this complication. Pregnant women with treated pulmonary AVMs appear to be at no higher risk for bleeding than pregnant women without pulmonary AVMs.

For generalized anemia, iron replacement and red blood cell transfusions may become necessary. People with OWR may develop medical problems unrelated to the condition, such as ulcers or colon cancer, which may cause additional GI blood loss.



The distended blood capillaries of this patient are visible on the face. These are referred to as telangiectases and are characterisic of Osler-Rendu-Weber syndrome. *(Photo Researchers, Inc.)*

Because telangiectases can occur in the mouth, dental work may be a particular problem for those with OWR. Bleeding in the mouth makes the oral area susceptible to oral bacteria, such as those on the gums. Bacteria can enter the bloodstream and cause infections in other areas of the body. The best preventive measure for this is to take antibiotics before any dental work in order to prevent infection. Additionally, medications such as aspirin and non-steroidal anti-inflammatory agents (such as Advil, Aleve, and Motrin) should be avoided because they can increase bleeding.

Since effective treatment measures are available, unaffected at-risk individuals in a family should be screened for symptoms of OWR, especially for brain, pulmonary, and GI AVMs.

Prognosis

Prognosis for individuals with OWR is good, assuming they receive appropriate and timely treatments. Because many treatments are effective, proper screening is crucial to prognosis.

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ORGANIZATIONS

HHT Foundation International, Inc. PO Box 8087, New Haven, CT 06530. (800) 448-6389 or (410) 584-7287. Canada: (604) 596-3418. Other countries: (914) 887-5844. Fax: (410) 584-7721 or (604) 596-0138. hhtinfo@hht.org. <http://www.hht.org>.

WEBSITES

Birth Disorder Information Directory. <http://www.bdid.com/owrs.htm>.

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Deepti Babu, MS

Osteoarthritis

Definition

Osteoarthritis is a degenerative joint disease characterized by the breakdown of the joint's cartilage.

Description

Osteoarthritis is one of the oldest and most common types of arthritis. With the breakdown of cartilage, the part of the joint that cushions the ends of bones, bones rub against each other, causing pain and loss of movement. Often called "wear-and-tear arthritis" or "old person's arthritis," many factors can cause osteoarthritis.

The biologic causes of the disorder are currently unknown. It does not appear to be caused by aging itself, although osteoarthritis generally accompanies aging. Osteoarthritic cartilage is chemically different from normal aged cartilage.

In many cases, certain conditions seem to trigger osteoarthritis. People with joint injuries from sports, work-related activity, or accidents may be at increased risk, and obesity may lead to osteoarthritis of the knees. Individuals with mismatched surfaces on the joints that could be damaged over time by abnormal stress may be prone to osteoarthritis. One study reported that wearing shoes with 2.5 in (6.3 cm) heels or higher may also be a contributing factor. High heels force women to alter the way they normally maintain balance, putting strain on the areas between the kneecap and thigh bone and on the inside of the knee joint.

Demographics

Osteoarthritis is estimated to affect more than 20 million Americans, mostly after age 45. Women are more commonly affected than men.

In the United States about 6% of adults over 30 have osteoarthritis of the knee and about 3% have osteoarthritis of the hip. Prevalence of osteoarthritis in most joints is higher in men than women before age 50, but after this age, more women are affected by osteoarthritis. The occurrence of the disease increases with age. In men, the hip is affected more often while in women, the hands, fingers, and knees are more problematic.

Some forms of osteoarthritis are more prevalent in African-American men and women than in Caucasians, possibly because they have a higher bone mineral density. In the case of knee osteoarthritis, it may be related to occupational and physical demands. African-American women also have a higher risk of developing bilateral knee osteoarthritis and hip osteoarthritis compared to women of other races. This difference may be because African-American women generally have a higher body mass index which puts more stress on the joints.

Osteoarthritis is common worldwide, although risk of osteoarthritis varies among ethnic groups. Caucasians have a higher risk than Asians, and the risk of osteoarthritis in the hips is lower in Asia and some Middle East countries than in the United States. Asians appear to have a higher incidence of osteoarthritis in the knee than Caucasians, however, and an equal risk in the spine. Location of affected joints and inherited forms of the disorder can influence age of onset.

Genetic profile

Genetics plays a role in the development of osteoarthritis, particularly in the hands and hips. One

study found that heredity may be involved in 30% of people with osteoarthritic hands and 65% of those with osteoarthritic knees. Another study found a higher correlation of osteoarthritis between parents and children and between siblings than between spouses. Other research has shown that a genetic abnormality may promote a breakdown of the protective structure in cartilage.

Abnormal collagen genes have been identified in some families with osteoarthritis. One recent study found that the type IX collagen **gene** COL9A1 (6q12-q13) may be a susceptibility locus for female hip osteoarthritis. Other research has suggested that mutations in the COL2A1 gene may be associated with osteoarthritis.

Some evidence also suggests that a female-specific susceptibility gene for idiopathic osteoarthritis is located on 11q. There is some evidence of genetic abnormality at the IL1R1 marker on gene 2q12 in individuals with severe osteoarthritis and Heberden nodes (bony lumps on the end joint of fingers).

Signs and symptoms

Although up to 85% of people over 65 show evidence of osteoarthritis on x ray, only 35-50% experience symptoms. Symptoms range from very mild to very severe, affecting hands and weight-bearing joints such as knees, hips, feet, and the back. The pain of osteoarthritis usually begins gradually and progresses slowly over many years.

Osteoarthritis is commonly identified by aching pain in one or more joints, stiffness, and loss of mobility. The disease can cause significant trouble walking and stair climbing. Inflammation may or may not be present. Extensive use of the joint often exacerbates pain in the joints. Osteoarthritis is often more bothersome at night than in the morning and in humid weather than dry weather. Periods of inactivity, such as sleeping or sitting, may result in stiffness, which can be eased by stretching and exercise. Osteoarthritis pain tends to fade within a year of appearing.

Bony lumps on the end joint of the finger, called Herberden's nodes, and on the middle joint of the finger, called Bouchard's nodes, may also develop.

Diagnosis

A diagnosis of osteoarthritis is made based on a physical exam and history of symptoms.

X rays are used to confirm diagnosis. In people over 60, the disease can often be observed on x ray. An indication of cartilage loss arises if the normal space between the bones in a joint is narrowed, if there is an abnormal increase in bone density, or if bony projections or erosions are evident. Any cysts that might develop in osteoarthritic joints are also detectable by x ray.

KEY TERMS

Cartilage—Supportive connective tissue which cushions bone at the joints or which connects muscle to bone.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Corticosteroids—Anti-inflammatory medications. Related to cortisol, a naturally produced hormone that controls many body functions.

Additional tests can be performed if other conditions are suspected or if the diagnosis is uncertain. Blood tests can rule out rheumatoid arthritis or other forms of arthritis.

It is possible to distinguish osteoarthritis from other joint diseases by considering a number of factors together:

- Osteoarthritis usually occurs in older people.
- It is usually located in only one or a few joints.
- The joints are less inflamed than in other arthritic conditions.
- Progression of pain is almost always gradual.

A few of the most common disorders that might be confused with osteoarthritis are rheumatoid arthritis, chondrocalcinosis, and Charcot's joints.

Treatment and management

There is no known way to prevent osteoarthritis or slow its progression. Some lifestyle changes can reduce or delay symptoms. Treatment often focuses on decreasing pain and improving joint movement. Prevention and treatment measures may include:

- Exercises to maintain joint flexibility and improve muscle strength. By strengthening the supporting muscles, tendons, and ligaments, regular weight-bearing exercise helps protect joints, even possibly stimulating growth of the cartilage.
- Joint protection, which prevents strain and stress on painful joints.
- Heat/cold therapy for temporary pain relief.
- Various pain control medications, including corticosteroids and NSAIDs (nonsteroidal anti-inflammatory drugs such as aspirin, acetaminophen, ibuprofren, and naproxen). For inflamed joints that are not responsive to

NSAIDS, injectable glucocorticoids may be used. For mild pain without inflammation, acetaminophen may be used.

- Weight control, which prevents extra stress on weight-bearing joints. One study reported that weight loss seemed to reduce the risk for symptomatic osteoarthritis of the knee in women, and in another, women who lost 11 pounds or more cut their risk for developing osteoarthritis in half.
- Surgery may be needed to relieve chronic pain in damaged joints. Osteoarthritis is the most common indication for total joint replacement of the hip and knee.

New treatment findings

Studies have found that estrogen may promote healthy joints in women. Hormone replacement therapy may significantly reduce the risk in postmenopausal women, particularly in the knees.

It has been reported that deficiencies in vitamin D in older people may worsen their condition, so individuals with osteoarthritis should strive to get the recommended 400 IU a day. To protect bones, adults should also consume at least 1,000 mg of calcium daily.

Glucosamine and chondroitin sulfate are popular nutritional supplements that may diminish the symptoms of osteoarthritis. According to some reports, a daily dose of 750–1,500 mg of glucosamine and chondroitin sulfate may result in reduced joint pain, stiffness, and swelling, however these supplements are not approved by the Food and Drug Adminstration as effective treatment of osteoarthritis. A person with osteoarthritis should consult with a doctor before using dietary supplements to treat symptoms.

Prognosis

Osteoarthritis is not life threatening, but quality of life can deteriorate significantly due to the pain and loss of mobility that it causes. Advanced osteoarthritis can force the patient to forgo activities, even walking, unless the condition is alleviated by medication or corrected by surgery.

There is no cure for osteoarthritis, and no treatment alters its progression with any certainty. Only heart disease has a greater impact on work, and 5% of those who leave the work force do so because of osteoarthritis.

Resources

BOOKS

Grelsamer, Ronald P., and Suzanne Loebl, eds. *The Columbia Presbyterian Osteoarthritis Handbook.* New York: Macmillan, 1997.

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McAlindon, Tim. "Glucosamine for Osteoarthritis: Dawn of a New Era?" *Lancet* 357 (January 27, 2001): 247+.

ORGANIZATIONS

Arthritis Foundation. 1330 West Peachtree St., Atlanta, GA 30309. (800) 283-7800. <http://www.arthritis.org>.

WEBSITES

National Institute of Arthritis and Musculoskeletal and Skin Diseases. <http://www.nih.gov/niams>.

The Arthritis Research Institute of America. <http://www.preventarthritis.org>.

Jennifer F. Wilson, MS

Osteogenesis imperfecta

Definition

Osteogenesis imperfecta (OI) is a group of genetic diseases of collagen in which the bones are formed improperly, making them fragile and prone to breaking.

Description

Collagen is a fibrous protein material. It serves as the structural foundation of skin, bone, cartilage, and ligaments. In osteogenesis imperfecta, the collagen produced is abnormal and disorganized. This results in a number of abnormalities throughout the body, the most notable being fragile, easily broken bones.

There are four forms of OI, Types I through IV. Of these, Type II is the most severe, and is usually fatal within a short time after birth. Types I, III, and IV have some overlapping and some distinctive symptoms, particularly weak bones.

Genetic profile

Evidence suggests that OI results from abnormalities in the collagen **gene** COL1A1 or COL1A2, and possibly abnormalities in other genes. In OI Type I, II, and III, the gene map locus is 17q21.31-q22, 7q22.1, and in OI Type IV, the gene map locus is 17q21.31-q22.

OI is usually inherited as an autosomal dominant condition. In autosomal dominant **inheritance**, a single

abnormal gene on one of the autosomal **chromosomes** (one of the first 22 "non-sex" chromosomes) from either parent can cause the disease. One of the parents will have the disease (since it is dominant) and is the carrier. Only one parent needs to be a carrier in order for the child to inherit the disease. A child who has one parent with the disease has a 50% chance of also being a carrier and having the disease and a 50% chance of not inheriting the dominant gene, and thus not having the disorder.

In OI, the genetic abnormality causes one of two things to occur. It may direct cells to make an altered collagen protein and the presence of this altered collagen causes OI Type II, III, or IV. Alternately, the dominant altered gene may fail to direct cells to make any collagen protein. Although some collagen is produced by instructions from the normal gene, an overall decrease in the total amount of collagen produced results in OI Type I.

If both parents have OI caused by an autosomal dominant gene change, there is a 75% chance that the child will inherit one or both OI genes. In other words, there is a 25% chance the child will inherit only the mother's OI gene (and the father's unaffected gene), a 25% chance the child will inherit only the father's OI gene (and the mother's unaffected gene), and a 25% chance the child will inherit both parents' OI genes. Because this situation has been uncommon, the outcome of a child inheriting two OI genes is hard to predict. It is likely that the child would have a severe, possibly lethal, form of the disorder.

About 25% of children with OI are born into a family with no history of the disorder. This occurs when the gene spontaneously mutates in either the sperm or the egg before the child's conception. No triggers for this type of mutation are known. This is called a new dominant mutation. The child has a 50% chance of passing the disorder on to his or her children. In most cases, when a family with no history of OI has a child with OI, they are not at greater risk than the general population for having a second child with OI, and unaffected siblings of a person with OI are at no greater risk of having children with OI than the general population.

In studies of families into which infants with OI Type II were born, most of the babies had a new dominant mutation in a collagen gene. In some of these families, however, more than one infant was born with OI. Previously, researchers had seen this recurrence as evidence of recessive inheritance of this form of OI. More recently, however, researchers have concluded that the rare recurrence of OI to a couple with a child with autosomal dominant OI is more likely due to gonadal mosaicism. Instead of a mutation occurring in an individual sperm or egg, it occurs in a percentage of the cells that give rise to a parent's multiple sperm or eggs. This mutation, present in a percentage of his or her reproductive cells, can result in more than one affected child without affecting the parent with the disorder. An estimated 2–4% of families into which an infant with OI Type II is born are at risk of having another affected child because of gonadal mosaicism.

KEY TERMS

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Ligament—A type of connective tissue that connects bones or cartilage and provides support and strength to joints.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Sclera—The tough white membrane that forms the outer layer of the eyeball.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Demographics

OI affects equal numbers of males and females. It occurs in about one of every 20,000 births.

Signs and symptoms

Type I

This is the most common and mildest type. Among the common features of Type I are the following:

- Bones are predisposed to fracture, with most fractures occurring before puberty. People with OI type I typically have about 20–40 fractures before puberty.
- Stature is normal or near-normal.
- Joints are loose and muscle tone is low.
- Usually sclera (whites of the eyes) have blue, purple, or gray tint.
- Face shape is triangular.
- Tendency toward **scoliosis** (a curvature of the spine).
- Bone deformity is absent or minimal.
- Dentinogenesis imperfecta may occur, causing brittle teeth.

- Hearing loss is a possible symptom, often beginning in the early 20s or 30s.
- Structure of collagen is normal, but the amount is less than normal.

Type II

Sometimes called the lethal form, Type II is the most severe form of OI. Among the common features of Type II are the following:

- Frequently, OI Type II is lethal at or shortly after birth, often as a result of respiratory problems.
- Fractures are numerous and bone deformity is severe.
- Stature is small with underdeveloped lungs.
- Collagen is formed improperly.

Type III

Among the common features of Type III are the following:

- Bones fracture easily. Fractures are often present at birth, and x rays may reveal healed fractures that occurred before birth. People with OI Type III may have more than 100 fractures before puberty.
- Stature is significantly shorter than normal.
- Sclera (whites of the eyes) have blue, purple, or gray tint.
- Joints are loose and muscle development is poor in arms and legs.
- Rib cage is barrel-shaped.
- Face shape is triangular.
- Scoliosis (a curvature of the spine) is present.
- Respiratory problems are possible.
- Bones are deformed and deformity is often severe.
- Dentinogenesis imperfecta may occur, causing brittle teeth.
- Hearing loss is possible.
- Collagen is formed improperly.

Type IV

OI Type IV falls between Type I and Type III in severity. Among the common features of Type IV are the following:

- Bones fracture easily, with most fractures occurring before puberty.
- Stature is shorter than average.
- Sclera (whites of the eyes) are normal in color, appearing white or near-white.
- Bone deformity is mild to moderate.
- Scoliosis (curvature of the spine) is likely.
- Rib cage is barrel-shaped.
- Face is triangular in shape.
- Dentinogenesis imperfecta may occur, causing brittle teeth.
- Hearing loss is possible.
- Collagen is formed improperly.

Diagnosis

It is often possible to diagnose OI solely on clinical features and x ray findings. Collagen or **DNA** tests may help confirm a diagnosis of OI. These tests generally require several weeks before results are known. Approximately 10–15% of individuals with mild OI who have collagen testing, and approximately 5% of those who have **genetic testing**, test negative for OI despite having the disorder.

Diagnosis is usually suspected when a baby has bone fractures after having suffered no apparent injury. Another indication is small, irregular, isolated bones in the sutures between the bones of the skull (wormian bones). Sometimes the bluish sclera serves as a diagnostic clue. Unfortunately, because of the unusual nature of the fractures occurring in a baby who cannot yet move, some parents have been accused of child abuse before the actual diagnosis of osteogenesis imperfecta was reached.

Prenatal diagnosis

Testing is available to assist in prenatal diagnosis. Women with OI who become pregnant, or women who conceive a child with a man who has OI, may wish to explore prenatal diagnosis. Because of the relatively small risk (2–4%) of recurrence of OI Type II in a family, families may opt for ultrasound studies to determine if a developing fetus has the disorder.

Ultrasound is the least invasive procedure for prenatal diagnosis, and carries the least risk. Using ultrasound, a doctor can examine the fetus's skeleton for bowing of the leg or arm bones, fractures, shortening, or other bone abnormalities that may indicate OI. Different forms of OI may be detected by ultrasound in the second trimester. The reality is that when it occurs as a new dominant mutation, it is found inadvertantly on ultrasound, and it may be difficult to know the diagnosis until after delivery since other genetic conditions can cause bowing and/or fractures prenatally.

Chorionic villus sampling is a procedure to obtain chorionic villi tissue for testing. Examination of fetal collagen proteins in the tissue can reveal information about the quantitative or qualitative collagen changes that lead

to OI. When a parent has OI, it is necessary for the affected parent to have the results of his or her own collagen test available. Chorionic villus sampling can be performed at 10–12 weeks of pregnancy.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus, into the amniotic sac, and withdrawing a small amount of amniotic fluid. DNA can be extracted from the fetal cells contained in the amniotic fluid and tested for the specific mutation known to cause OI in that family. This technique is useful only when the mutation causing OI in a particular family has been identified through previous genetic testing of affected family members, including previous pregnancies involving a baby with OI. Amniocentesis is performed at 16–18 weeks of pregnancy.

Treatment and management

There are no treatments available to cure OI, nor to prevent most of its complications. Most treatments are aimed at correcting the fractures and bone abnormalities caused by OI. Splints, casts, braces, and rods are all used. Rodding refers to a surgical procedure in which a metal rod is implanted within a bone (usually the long bones of the thigh and leg). This is done when bowing or repeated fractures of these bones has interfered with a child's ability to begin to walk.

Other treatments include hearing aids and early capping of teeth. Patients may require the use of a walker or wheelchair. Pain may be treated with a variety of medications. Exercise is encouraged as a means to promote muscle and bone strength. Swimming is a form of exercise that puts a minimal amount of strain on muscles, joints, and bones. Walking is encouraged for those who are able.

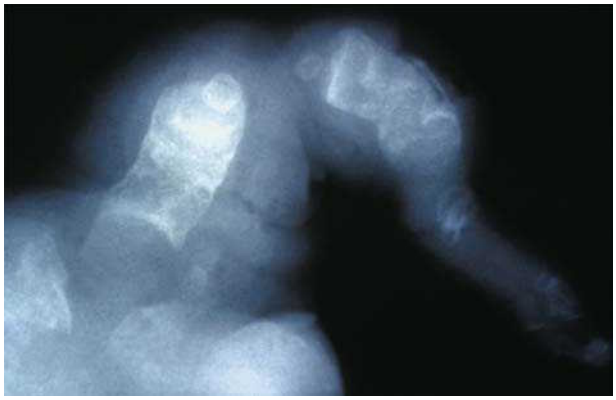
Smoking, excessive alcohol and caffeine consumption, and steroid medications may deplete bone and increase bone fragility.

Alternative treatment such as acupuncture, naturopathic therapies, hypnosis, relaxation training, visual imagery, and biofeedback have all been used to try to decrease the constant pain of fractures.

Prognosis

Lifespan for people with OI Type I, III, and IV is not generally shortened. The prognosis for people with these types of OI is quite variable, depending on the severity of the disorder and the number and severity of the fractures and bony abnormalities.

Fifty percent of all babies with OI Type II are stillborn. The rest of these babies usually die within a very short time after birth. In recent years, some people with Type II have lived into young adulthood.



Osteogenesis Imperfecta, radiograph of the left leg. X ray showing light spot and poor bone formation. Photo by Joseph R. Siebert, Ph. D. *(Custom Medical Stock Photo, Inc.)*

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Jennifer F. Wilson, MS

Osteoporosis

Definition

Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissues, leading to bone fragility and, consequently, an increase in fracture risk.

Description

The term osteoporosis comes from the Greek word *osteon*, meaning bone, and *porus*, meaning pore or passage. Osteoporosis literally makes bones porous. The amount of calcium stored in bones decreases over time causing the skeleton to weaken.

In the body of early adults, both the mineral portion and the framework of bone is in constant flux. Old tissue is broken down and reabsorbed and new bone is created at approximately the same rate. In later years, this rate of renewal begins to slow behind the rate of removal. This slowing is what leaves the bones thinner and more fragile. The most typical sites of fractures related to osteoporosis are the hip, spine, wrist, and ribs, although the disease can affect any bone in the body.

The average woman acquires 98% of her skeletal mass by approximately age 20. Building strong bones during childhood and adolescence is a key defense against developing osteoporosis later. There are four main steps to preventing osteoporosis: consuming a balanced diet rich in calcium and vitamin D; participating in weight-bearing exercise; following a healthy lifestyle, including no smoking and limited alcohol intake; and testing bone density and taking medication when appropriate.

Type I, postmenopausal osteoporosis, is the most common. It is usually a consequence of reproductive hormone deficiency, and afflicts mostly women over age 50. The disorder typically appears within the first ten or twenty years after menopause. Men may also develop the disorder, usually around 50-60 years of age, as a result of:

- Prolonged exposure to certain medications such as steroids used to treat **asthma** or arthritis, anticonvulsants, aluminum-containing antacids, and certain **cancer** treatments
- Chronic disease that affects the kidneys, lungs, stomach, and intestines and alters hormone levels
- Undiagnosed low levels of the sex hormone testosterone
- Lifestyle habits such as smoking, excessive alcohol use, low calcium intake, inadequate physical exercise

Type II, senile osteoporosis, affects both men and women over the age of 70, although women are twice as likely to develop the disorder.

In some cases, osteoporosis is secondary to another cause. It can accompany endocrine disorders such as **acromegaly** and Cushing syndrome. It results from excessive use of drugs such as corticosteroids. In these cases, the treatment is directed at curing the principal ailment or at not using the offending drug. Blood or urine tests will diagnose other causes of bone loss or bone density.

Genetic profile

Osteoporosis results from a complex interaction between genetic and environmental factors throughout life. Evidence suggests that peak bone mass is inherited, but current genetic markers are only able to explain a small proportion of the variation in individual bone mass or fracture risk. At this time, no specific mode of **inheritance** has been identified. Heritability of bone mass has been estimated to account for 60-90% of its variance. Studies have shown reduced bone mass in daughters of osteoporotic women when compared with controls; in men and women who have first-degree relatives with osteoporosis; and in perimenopausal women who have a family history of hip fracture. Body weight in infancy may be a determinant of adult bone mineral area.

Some scientists think that environmental influences during early life interact with the genome to establish the functional level of a variety of metabolic processes involved in skeletal growth.

Many candidate genes exist for osteoporosis, however relatively few have been studied. The first candidate **gene** to be identified was the vitamin D receptor (VDR) gene, and studies are ongoing as to how much this gene accounts for variance in bone mass. The response of bone mass to dietary supplementation with vitamin D and calcium is known to be dependent, in part, on VDR polymorphisms. Other genes may aid in establishing who would benefit from treatments like hormone replacement therapy, bisphosophonates, or exercise. Associations between bone mass and polymorphisms have also been found in the estrogen receptor gene, the interleukin-6 genes, the transforming growth factor beta, and a binding site of the collagen type I alpha1 (COLIA1) gene.

The risk of osteoporosis is greatly determined by peak bone mass, and any gene linked to fractures in the elderly may possibly be associated with low bone mass in children as well.

Environmental influences such as diet, climate, and physical exercise may have significant impact on gene expression, as well. In particular, malnutrition early in life is likely to have permanent effects resulting in lowered bone mass.

Demographics

Significant risk has been reported in people of all ethnic backgrounds. Asian and white women are at greatest risk of bone thinning because they generally have the lowest bone density. Although the risk is smaller, African-American and Hispanic-American women should take percaution, as well. An estimated 10% of African-American women over age 50 have osteoporosis and an additional 30% have low bone density that puts them at risk of developing osteoporosis.

Women in general have a four times greater risk than men of developing osteoporosis, and 80% of those affected by osteoporosis are women. In the United States, an estimated eight million American women and two million men have osteoporosis.

An osteoporosis-related fracture will occur in one in two women and one in eight men over the age of 50.

Signs and symptoms

Often called "the silent disease" because bone loss occurs without symptoms, people may not know that they have osteoporosis until they have a fracture from a minor bump or fall, or a vertebra collapses. Physical signs of osteoporosis include back pain, loss of height over time, stooped posture, and fractures of vertebrae, wrists, or hips. Osteoporosis can be detected by a bone mineral density test or even a regular x ray.

Without preventive treatment, women can lose up to 20% of their bone mass in the first five to seven years following menopause, making them more susceptible to osteoporosis.

Over many years, a sequence of spinal compression fractures may cause kyphosis, the bent-over posture known as dowager's or widow's hump. These fractures rarely require surgery, and they can range from causing minor discomfort to severe painful episodes of backache. In either case, pain generally subsides gradually over one to two months.

Diagnosis

Since osteoporosis can develop undetected for decades until a fracture occurs, early diagnosis is important.

A bone mineral density test (BMD) is the only way to diagnose osteoporosis and determine risk for future fracture. The painless, noninvasive test measures bone density and helps determine whether medication is needed to help maintain bone mass, prevent further bone loss, and reduce fracture risk.

KEY TERMS

Corticosteroids—Anti-inflammatory medications. Related to cortisol, a naturally produced hormone that controls many body functions.

Menopause—Cessation of menstruation in the human female, usually occurring between the ages of 46 and 50.

Osteopenic—Bone density that is somewhat low, but not osteoporotic.

Polymorphism—A change in the base pair sequence of DNA that may or may not be associated with a disease.

Several different machines measure bone density. Central machines, such as the dual energy x-ray absorptiometry (DXA or DEXA) and quantitative computed tomography (QCT), measure density in the hip, spine and total body. Peripheral machines, such as radiographic absorptiometry (RA), peripheral dual energy x-ray absorptiometry (pDXA), and peripheral quantitative computed tomography (pQCT), measure density in the finger, wrist, kneecap, shin bone, and heel.

A physician may be able to observe osteoporotic bone in a routine spinal x ray, however, BMD tests are more accurate and can measure small percentages of lost bone density. In an x ray, osteoporotic bone appears less dense and the image is less distinct, suggesting weaker bone.

There are no official guidelines for osteoporosis screening. Some physicians recommend bone density testing at menopause to begin preventive treatment if necessary. Generally, testing is recommended for postmenopausal women who have suffered a bone fracture after menopause or who have gone through menopause and have at least one risk factor for the disease. The major risk factors are low body weight, low calcium intake, poor health, and a history of osteoporosis in the family. The test is usually recommended for all women over 65.

Testing may also be recommended for elderly men with one of the following risk factors: bone fracture, poor health, or low testosterone levels.

Treatment and management

There a number of options for preventing and treating bone loss.

Bone atrophy due to osteoporosis in a human femur. The ball joint has become porous and brittle. *(Custom Medical Stock Photo, Inc.)*

Therapeutic options

Various therapies have been shown to be effective in preventing bone loss and increasing bone mass. These include:

- *Estrogen.* For women with postmenopausal osteoporosis, estrogen replacement therapy helps halt bone loss and exerts a modest bone-building effect. Stopping estrogen therapy restarts bone loss, so long-term treatment is usually recommended. For women entering menopause, some physicians recommend estrogen replacement therapy to replace the decreasing supply of naturally-occurring estrogen in the body and enable the skeleton to slow its rate of absorption and retain calcium. Estrogen is considered the best treatment against osteoporosis. Physicians may recommend combination estrogen and progesterone replacement therapy in women who have an intact uterus in order to reduce endometrial cancer risk. Some studies indicate a relationship between estrogen use and **breast cancer** while other studies indicate no relationship at all; the issue is still to be determined.
- *Raloxifene.* One of a class of drugs called selective estrogen receptor modulators (SERMs) that appear to prevent bone loss, raloxifene (Evista) produces small increases in bone mass. It is approved for the prevention and treatment of osteoporosis. Like estrogens, SERMs produce changes in blood lipids that may protect against heart disease, although the effects are not as potent as that of estrogen. Unlike estrogens, SERMs do not appear to stimulate uterine or breast tissue.
- *Alendronate.* One of a class of medications called bisphosphonates, alendronate (Fosamax) may prevent bone loss, increase bone mass, and reduce the risk of fractures.
- *Risedronate.* Also from the bisphosphonate family, risedronate (Actonel) has been shown to reduce bone loss, increase bone density, and reduce the risk of fractures.
- *Calcitonin.* A hormone that regulates calcium levels in the blood, calcitonin and may prevent bone loss. It is approved for treatment of diagnosed osteoporosis.

Preventive options

Measures have been identified that improve bone strength over the life span. Physicians recommend that all adult men and women, but particularly men and women over the age of 50, take the following measures to prevent osteoporosis:

- Consume at least 1,000 mg calcium. Foods high in calcium include dairy products, leafy green vegetables, beans, nuts and whole-grain cereals. Supplements may be taken if adequate intake cannot be achieved through diet.
- Consume 400 IU of vitamin D to enhance calcium absorption.
- Participate in regular weight-bearing exercise, such as walking, jogging, tennis, weight-lifting, and cross-county skiing, to strengthen bones.
- Stop smoking.
- Reduce intake of caffeine to not more than three cups a day.
- Limit alcohol to not more than two drinks per day.
- Avoid excessive amounts of dietary fiber as it binds to calcium and may interfere with absorption.

Making the house a safer place against falls can decrease risk of fracture in people with osteoporosis. Install handrails on the stairs; remove loose throw rugs; keep rooms and hallways well-lit including night lights; install handrails beside the tub, shower and toilet; place

nonskid mats in the bathtub, shower, and on tile bathroom floors.

If fractures occur, treatment may require casts, braces, physical therapy and surgery to assist bone healing.

Prognosis

When osteoporosis is untreated, it can cause serious disability. Osteoperosis can be managed with proper medical and self-care.

Osteoporosis is associated with 40,000 deaths annually, mostly from complications of surgery or immobilization after hip fractures.

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Foundation for Osteoporosis Research and Education. 300 27th St., Oakland, CA 94612. (888) 266-3015. <http://www.fore.org>.

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Jennifer F. Wilson, MS

Otopalatodigital syndrome

Definition

Otopalatodigital (OPD) syndrome, also called digitootopalatal syndrome or palatootodigital syndrome, is a rare X-linked genetic disorder that affects bone and facial structure. OPD is fully expressed in males. Females are only mildly affected.

Description

There are two forms of OPD syndrome. Type I is inherited through an X-linked trait with intermediate expression in females while type II is inherited through an X-linked recesssive trait. OPD syndrome type I is also called Taybi syndrome. OPD syndrome type II is alternately called Andre syndrome, cranioorodigital syndrome, or faciopalatoosseous (FPO) syndrome.

A genetic disorder called frontometaphyseal **dysplasia**, or FMD, has very similar features to type I OPD syndrome.

There are three recognized forms of a genetic disorder called **Larsen syndrome**: an autosomal dominant type, a recessive type, and a lethal type. All three of these syndromes have similar symptoms to those seen in individuals affected with OPD syndrome. Recent evidence also suggests that Larsen syndrome, recessive type, may in fact be type II OPD syndrome.

As the various names of OPD syndrome suggest, this disorder is characterized by malformations and/or dysfunctions of the ears (-oto-), palate (-palato-), fingers and toes (-digito-), skull (-cranio-), mouth (-oro-), face (-facio-), and bones (-osseo-). Some of the characteristics common to both types of OPD syndrome include: a cleft palate, a prominent forehead, a broad nose, widely spaced eyes (hypertelorism), a downward slanting of the opening between the upper and lower eyelids (palpebral fissures), conductive hearing loss, short fingers and toes (**brachydactyly**), an abnormal inward curving of the fingers (clinodactyly), a caved in chest at birth (pectus excavatum); short stature (dwarfism), and a congenital dislocation of the elbows caused by a misalignment of the head of the large bone in the forearm (radius).

Genetic profile

Both forms of OPD syndrome are X-linked. The **gene mutation** responsible for the appearance of type I OPD syndrome has been tentatively assigned to the Xq28 band. It is also believed that type II OPD syndrome is an allelic variant of type I OPD, which is to say that each form of OPD syndrome is caused by different mutations in the same **gene** or in overlapping genes at the same chromosomal location. Recessive type Larsen syndrome is also believed to be either another allelic variant of OPD syndrome, or identical to type II OPD syndrome. Another extremely rare genetic disorder, Melnick-Needles syndrome also has an overlapping of symptoms with type II OPD syndrome. It is felt that this syndrome is also possibly an allelic variant of OPD syndrome.

OPD syndrome is transmitted via the X chromosome. A female generally possesses two X **chromosomes**,

KEY TERMS

Brachydactyly—Abnormal shortness of the fingers and toes.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Clinodactyly—An abnormal inward curving of the fingers or toes.

Conductive hearing loss—Hearing loss that is the result of a dysfunction of the parts of the ear responsible for collecting sound. In this type of hearing loss, the auditory nerve is generally not damaged.

Hypertelorism—A wider-than-normal space between the eyes.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Omphalocele—A birth defect where the bowel and sometimes the liver, protrudes through an opening in the baby's abdomen near the umbilical cord.

Palpebral fissures—The opening between the upper and lower eyelids.

Pectus excavatum—An abnormality of the chest in which the sternum (breastbone) sinks inward; sometimes called "funnel chest."

one from her mother and one from her father. A male generally possesses only a single X chromosome, that from his mother. He gets a Y chromosome from his father. Certain rare exceptions to these **inheritance** patterns are seen, but in general, a female is an XX and a male is an XY. It is for this reason that X-linked disorders are generally seen in greater numbers of males than females. The male does not possess a second X chromosome that can be expressed. A male either has a mutation on his X chromosome, or he does not. A female, on the other hand, can be either homozygous or heterozygous for an X-linked trait. That is, she can either have two identical copies of this trait (homozygous) or only one copy is this trait (heterozygous).

Type I OPD syndrome is transmitted through a dominant trait. A child of a type I OPD syndrome affected parent has a 50% chance of also being affected with type I OPD syndrome.

Type II OPD syndrome is transmitted through an X-linked recessive trait. A child of a type II OPD syndrome affected parent has a 50% chance of also inheriting the gene for the type II OPD syndrome. Subsequently, if that child is male, he will have expression of the disorder. If it is a female child, then she generally will have milder features. Girls who are homozygous for type II OPD syndrome (inheriting the gene from each parent) will exhibit more severe symptoms than girls who are heterozygous for type II OPD syndrome. Males affected with type II OPD syndrome exhibit symptoms similar to those seen in homozygous girls.

Demographics

As of early 2001, the incidence of occurrence of both forms of OPD syndrome has not been determined. The lack of occurrence rate data is partially due to the fact that type I OPD syndrome can often have only very mild clinical and radiological symptoms, such that it is often not diagnosed, or even noticed, until type I OPD syndrome is recognized in a more severely affected member of the family.

Type I OPD syndrome is more common than type II OPD syndrome, and as of early 2001, nearly 300 cases had been reported in the medical literature. In 1996, only 25 detailed cases of type II OPD syndrome had been described in the medical literature.

Signs and symptoms

The severity of symptoms experienced by those people affected with OPD syndrome varies widely from practically asymptomatic to symptoms so severe that they cause infantile or prenatal death. In type II OPD syndrome, males are generally affected with far more severe symptoms than females.

There are six abnormalities of the face and head that characterize OPD syndrome: a cleft palate, downwardly slanting openings between the eyelids, widely spaced eyes (hypertelorism), a prominent forehead, a broad nose, and conductive hearing loss.

Conductive hearing loss results from a blockage of the auditory canal or some other dysfunction of the eardrum or one of the three small bones within the ear (the stapes, the malleus, and the incus) that are responsible for collecting sound. In this type of hearing loss, the auditory nerve is normal. In individuals affected with OPD syndrome, complete deafness from birth is often observed. In those individuals with partial hearing, speech disabilities related to this hearing loss are quite common.

In addition to the abnormalities of the head, universal characteristics of OPD syndrome affected individuals also include: abnormally short fingers and toes (brachydactyly); abnormal inward curving of some fingers (clinodactyly); short nails; a congenital dislocation of the elbows, and sometimes the knees; a caved in chest (pectus excavatum) at birth; and, growth retardation.

Symptoms that are characteristic of type I OPD syndrome include: curvature of the spine (**scoliosis**); generalized bone malformation, particularly in the bones of the limbs and ribcage; broad distal digits, malformed or missing teeth (hypodontia); and, mild mental retardation.

Symptoms that are characteristic of type II OPD syndrome include: low-set ears, flattened vertebrae in the spine, bowing of the bones of the limbs, flexed overlapping digits, a malformation or complete absence of the large bone in the shin (fibula), malformations of the hips, a small opening in the abdominal wall (hernia) at the navel (**omphalocele**), and a malformation of the male genitalia in which the opening of the urethra is located on the underside of the penis, rather than at the tip of the penis (hypospadias).

Diagnosis

A diagnosis of OPD syndrome is suggested when a patient presents the five characteristic abnormalities of the head and face accompanied by conductive hearing loss. This diagnosis is confirmed by the observance of brachdactyly and congenital dislocation of the elbows and/or knees.

Type I OPD syndrome is differentially diagnosed from type II OPD syndrome by the appearance of scoliosis. Type II OPD syndrome is differentially diagnosed from type I OPD by the presence of an omphalocele and greater malformations of the bones of the ribcage.

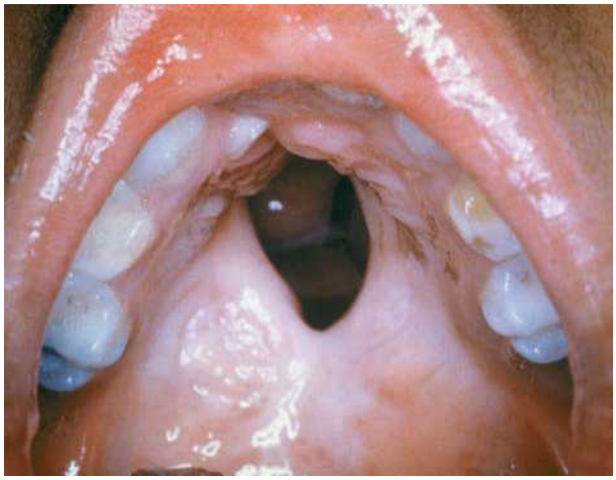
Treatment and management

There are currently no treatments aimed specifically at OPD syndrome. Instead, treatment is on a case-by-case and symptom-by-symptom basis.

Malformations of the head and face can generally be corrected, if necessary, by surgeries. In certain instances, the conductive hearing loss experienced by individuals with OPD syndrome may also be corrected through surgery. When it cannot, hearing aids may be required.

Many of the skeletal abnormalities seen in OPD syndrome affected individuals can either be corrected by surgery or can be alleviated through the use of braces until the bones become more fully developed.

Malformations of the male genitalia and the omphalocele observed in type II OPD syndrome affected infants can also be corrected by surgery.



Cleft palate results in an opening of the roof of the mouth. This facial abnormality is one of several characteristics that define otopalatodigital syndrome. *(Photo Researchers, Inc.)*

Certain OPD affected individuals may also benefit from treatments with growth hormone.

In cases of mild mental retardation or speech problems, early intervention programs for these types of developmental delays may also be of benefit.

Prognosis

Most individuals affected with type I OPD syndrome can expect to lead full lives if medical treatments, including corrective surgeries, are sought. Many individuals affected with type II OPD syndrome die either prior to birth or as infants due to respiratory failure associated with the malformation of the bones of the ribcage. If these individuals survive infancy, they also may expect to live full lives after corrective surgeries and other medical treatments.

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ORGANIZATIONS

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

FACES: The National Craniofacial Association. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

Let's Face It (USA) PO Box 29972, Bellingham, WA 98228-1972. (360) 676-7325. letsfaceit@faceit.org. <http://www.faceit.org/letsfaceit>.

National Foundation for Facial Reconstruction. 317 East 34th St. #901, New York, NY 10016. (800) 422-3223. <http://www.nffr.org>.

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Paul A. Johnson

Ovarian cancer

Definition

Ovarian cancer is a disease in which the cells in the ovaries become abnormal and start to grow uncontrollably, forming tumors. Ninety percent of all ovarian cancers develop in the cells that line the surface of the ovaries and are called "epithelial cell tumors."

Description

The ovaries are a pair of almond-shaped organs that lie in the pelvis on either side of the uterus. The fallopian tubes connect the ovaries to the uterus. The ovaries produce and release an egg each month during a woman's menstrual cycle. In addition, they also produce the female hormones estrogen and progesterone, which regulate and maintain the proper growth and development of female sexual characteristics.

Ovarian cancer is the fifth most common cancer among women in the United States. It accounts for 4% of all cancers in women. However, ovarian cancer is very difficult to discover in the early stages. This is often because there are no obvious warning signs, and the disease can grow relatively quickly. In addition, the ovaries are situated deep in the abdomen and small tumors may not be detected easily during a routine physical examination. Because of this, the death rate due to ovarian cancer is higher than that of any other cancer among women, since it may only be detected at advanced stages.

Ovarian cancer can develop at any age, but more than half the diagnoses are among women who are 60 years or older. The vast majority of people with ovarian cancer have no family history of the disease. However, for about 5-10% of individuals, there may be a very strong family history of ovarian cancer or other cancers, such as **breast cancer**. In these cases, a specific genetic alteration may be in the family, causing a predisposition to ovarian cancer and other associated cancers.

Genetic profile

Cells in ovarian tissue normally divide and grow, according to controls and instructions by various genes. If these genes have changes within them, the instructions for cellular growth and division may go awry. Abnormal, uncontrolled cell growth may occur, causing ovarian cancer. Therefore, all ovarian cancers are genetic because they all result from changes within genes. The difference is that most ovarian cancers are caused by sporadic changes within the genes, and only a minority are caused by inherited genetic alterations. Most ovarian cancers occur later in life after years of exposure to various environmental factors (such as the body's own hormones, asbestos exposure, or smoking) that can cause sporadic genetic alterations.

A small proportion of ovarian cancer is caused by inherited genetic alterations. As of 2001, a genetic alteration causing a predisposition solely to ovarian cancer has not yet been identified. However, in 1994 a breast and ovarian cancer susceptibility **gene**, known as BRCA1 (location 17q21), was identified. The discovery of BRCA2 (location 13q12) followed shortly in 1995. Women with alterations in these genes have an increased risk for breast and ovarian cancer, and men have an increased risk for **prostate cancer**. Men with a BRCA2 alteration have an increased risk for breast cancer. Slightly increased risks for colon and pancreatic cancers (in men and women) are also associated with BRCA2 alterations.

BRCA1 and BRCA2 alterations are inherited in an autosomal dominant manner; an individual who has one copy of a BRCA alteration has a 50% chance to pass it on to each of his or her children, regardless of that child's gender. Nearly all individuals with BRCA alterations have a family history of the alteration, usually a parent with it. In turn, they also may have a very strong family history of breast, ovarian, prostate, colon, and/or pancreatic cancers. Aside from BRCA1 and BRCA2, there

likely are other cancer susceptibility genes that are still unknown.

In addition to BRCA1 and BRCA2, ovarian cancer may be present in rare genetic cancer syndromes. In these instances, an individual may have other health problems (unrelated to cancer) and a family history of a wide variety of cancers and symptoms. As an example, Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is a syndrome that often involves cancers of the colon, uterus, ovaries, and stomach. HNPCC is due to changes in several genes including hMLH1, hMSH2, hMSH6, and hPMS2. These genes are unrelated to BRCA1 and BRCA2.

Demographics

On average, a North American woman faces a lifetime risk of approximately 2% to develop ovarian cancer. The incidence of ovarian cancer is higher among Caucasian women. The American Cancer Society states that in the year 2000 about 23,100 new cases of ovarian cancer will be diagnosed in the United States, and 14,000 women will die from the disease. Specific BRCA alterations are common in certain ethnic groups, which may make hereditary ovarian cancer more common in these populations. As of 2001, certain BRCA alterations are more common in the Ashkenazi (Eastern European) Jewish, Icelander, Dutch, French Canadian, and West African populations.

Signs and symptoms

Ovarian cancer has no specific signs or symptoms in the early stages of the disease. However, one may experience some of the following:

- Pain or swelling in the abdominal area
- Bloating and general feeling of abdominal discomfort
- Constipation, nausea, or vomiting
- Loss of appetite, tiredness
- Unexplained weight gain (generally due to fluid building up from the cancer in the abdomen)
- Vaginal bleeding in women who have already gone through menopause

Only a physician can assess whether or not the symptoms are an indication of early ovarian cancer. This is why it is important for a physician to be informed right away if any of the above symptoms are present.

A family history of ovarian cancer puts a woman at an increased risk for developing the disease. In addition, if a woman has had, or has a family history of breast cancer she may be at an increased risk for ovarian cancer. Signs of a possible BRCA1 or BRCA2 alteration in a family, signifying hereditary breast or ovarian cancer, include:

- Several relatives with cancer
- A large number of relatives with cancer versus unaffected relatives
- Close genetic relationships between people with cancer, such as parent-child, sibling-sibling
- Earlier ages of cancer onset, such as before ages 45-50
- An individual with both breast and ovarian cancer
- An individual with bilateral or multi-focal breast cancer
- The presence of ovarian, prostate, colon, or pancreatic cancers in the same family

KEY TERMS

Alteration—Change or mutation in a gene, specifically in the DNA that codes for the gene.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Laparoscopy—A diagnostic procedure in which a small incision is made in the abdomen and a slender, hollow, lighted instrument is passed through it. The doctor can view the ovaries more closely through the laparoscope, and if necessary, obtain tissue samples for biopsy.

Laparotomy—An operation in which the abdominal cavity is opened up.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Pelvic examination—Physical examination performed by a physician, often associated with a Pap smear. The physician inserts his/her finger into a woman's vagina, attempting to feel the ovaries directly.

Transvaginal ultrasound—A way to view the ovaries using sound waves. A probe is inserted into the vagina and the ovaries can be seen. Color doppler imaging measures the amount of blood flow, as tumors sometimes have high levels of blood flow.

• Case(s) of breast cancer in men

Suspicion of a BRCA alteration may be raised if someone has the above features in their family and they are of a particular ethnic group, such as Ashkenazi Jewish. This is because specific BRCA1 and BRCA2 alterations are known to be more common in this group of individuals.

Diagnosis

If a woman has symptoms of ovarian cancer, a pelvic examination is usually conducted to feel the ovaries to see if they have enlarged, indicative of a tumor. Blood tests to determine the level of a protein, known as carbohydrate antigen 125 (CA-125), may be done. CA-125 blood levels can be high when a woman has ovarian cancer. Additionally, a pelvic or transvaginal ultrasound (with color Doppler imaging) may be used to get several views of the ovaries, carefully checking their shape and structure. A CT scan may be helpful if the ultrasound is technically unsatisfactory for accurate interpretation.

A biopsy and surgery is necessary in order to determine the type of tumor, as not all tumors are cancerous. If the tumor appears to be small, a procedure known as laparoscopy may be used. A tiny incision is made in the abdomen and a slender, hollow, lighted instrument is inserted through it. This enables the doctor to view the ovary more closely and to obtain a biopsy. If the ovary has suspicious findings on laparoscopy and biopsy, a laparotomy (open surgery performed under general anesthesia) and removal of that ovary is usually performed. Large masses are investigated by open surgery.

Standard imaging techniques such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) may be used to determine if the disease has metastasized (spread) to other parts of the body.

As of 2001, there is DNA-based **genetic testing** to identify a BRCA1 or BRCA2 alteration in an individual. In the United States, Myriad Laboratories in Utah is the only place to offer this costly testing (as of 2001, it is about $2,700 for initial analysis). A blood sample is used, and both BRCA genes are studied for alterations. There is also targeted testing for people in high-risk ethnic groups (such as Ashkenazi Jewish) in which only the common BRCA alterations can be tested. Even with current technology (as of 2001), only certain regions of the BRCA genes can be studied, which leaves some alterations unable to be found.

For women without cancer who test positive for a BRCA alteration, this now places them at a significantly increased risk to develop the associated cancers. A woman's risks associated with a BRCA1 alteration are: 40-60% for ovarian cancer by age 70 and 3-85% for breast cancer by age 70. A woman's risks with a BRCA2 alteration are: 16-27% for ovarian cancer by age 70 and 4-86% for breast cancer by age 70.

For women with ovarian cancer who are found to have a BRCA alteration, this now places them at an increased risk to develop breast cancer. For some women, this may be a new risk they were not aware of before the testing, particularly if they have no family history of breast cancer.

For all women with a BRCA2 alteration, there may be a slightly increased risk for colon and pancreatic cancers. Additionally, because the testing process and test results are quite complex (and may have strong emotional consequences) everyone should receive proper **genetic counseling** before pursuing any BRCA1 and BRCA2 testing. Prenatal BRCA testing is available, but is rarely performed unless accompanied by extensive genetic and psychological counseling.

Treatment and management

As with many other cancers, treatment is determined by the exact size and type of ovarian cancer, so it is often unique to an individual. However, the cornerstone of treatment for ovarian cancer is surgery. This may require a laparotomy procedure in order to remove as much cancerous tissue as possible. Other organs, such as the uterus and fallopian tubes, may also be removed (especially if the cancer has spread there). Chemotherapy, the use of strong chemicals to kill cancer cells, is usually done following surgery. The purpose is to destroy any remaining cancer cells. Radiation therapy (using radioactive waves to kill cancer cells) is not typically used for ovarian cancer because it is not as effective as other treatments.

Screening recommendations for women at high risk to develop ovarian cancer (such as those with a strong family history of the disease) may include:

• Pelvic examination every six months or yearly, starting at age 25-35

• Transvaginal ultrasound with color Doppler imaging every six months or yearly, beginning at age 25-35

• Yearly blood CA-125 testing, starting at age 25-35

For women with a BRCA1 or BRCA2 alteration, they are also at an increased risk for breast cancer. Screening recommendations for them may include:

• Examining their own breasts monthly

• Examination of their breasts by a physician/nurse every six months or yearly, starting at age 25-35

• Mammograms (x rays of the breasts) yearly, starting at age 25-35

Specific screening programs may vary by physician. In addition to cancer screening, women with BRCA1 or BRCA2 alterations should know about their preventive surgery options. They may consider having their healthy ovaries and/or breasts removed, in order to reduce their risks to develop ovarian and/or breast cancer. Women may be more agreeable to having their ovaries removed because ovarian cancer is difficult to detect. However, this ends their ability to have children and automatically begins menopause for them. Both preventive surgeries greatly reduce a woman's cancer risk, but they can never eliminate the risk entirely.

For people with cancer or at high risk for it, there often are support and discussion groups available. These may be invaluable for those who feel alone in their situation, because they can meet others who are dealing with the exact same issues.

Prognosis

Because ovarian cancer is not usually diagnosed until it is in an advanced stage, it is the most deadly of all the female cancers of the reproductive organs. As of 2000, only 46% of women diagnosed with ovarian cancer will survive past five years. If ovarian cancer is diagnosed before it has spread to other organs, more than 90% of the patients will survive five years or more. Unfortunately, only 24% of all cancers are found at this early stage.

As of 2001, there appears to be no difference in how a woman with ovarian cancer will do, whether or not she has a BRCA alteration. Because unaffected people in a family with a BRCA alteration may be in high-risk screening programs, the hope is that they may be able to have any of their cancers detected earlier, giving a better prognosis.

Resources

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ORGANIZATIONS

American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

Facing Our Risk of Cancer Empowered (FORCE). 934 North University Drive, PMB #213, Coral Springs, FL 33071. (954) 255-8732. info@facingourrisk.org. <http://www.facingourrisk.org>.

Gilda's Club. 195 West Houston Street, New York, NY 10014. (212) 647-9700. Fax: (212) 647-1151. <http://www.gildasclub.org>.

Gynecologic Cancer Foundation. 401 North Michigan Avenue, Chicago, IL 60611. (800) 444-4441.

National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda, MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

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National Ovarian Cancer Coalition. <http://www.ovarian.org>.

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Deepti Babu, MS

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P

Paine syndrome

Definition

Paine syndrome is a rare genetic condition that is present at birth. Characterized by an undersized head and related abnormalities in the brain, the disease results in severe mental and physical retardation, movement disorders, and vision problems. Most infants with Paine syndrome do not survive their first year of life.

Description

The cerebellum, which is Latin for "little brain," is the part of the brain that controls involuntary movements, such as maintaining balance and coordinating muscles during physical activity. When shaking hands, for example, the cerebellum plays a primary role in coordinating the dozens of muscles involved in this seemingly simple task. Paine syndrome, which is named after the American pediatrician who first described the condition in 1960, interferes with the proper growth of the cerebellum and other parts of the brain while the fetus is still in the womb. Though this syndrome is considered a single entity, it actually includes several disorders that emerge together. The result is a variety of debilitating effects.

Children born with Paine syndrome have microcephaly. This neurological disease, which is also associated with conditions other than Paine syndrome, is characterized by an abnormally small head. The head of an infant with microcephaly is smaller than average when compared to other babies of the same age and gender. This decreased skull size is an indication that the brain did not grow properly during fetal development. The form of microcephaly associated with Paine syndrome causes physical and mental retardation. Aside from a small head, infants with Paine syndrome may have undersized bodies. Motor skills, language abilities, and other aspects of normal development are impaired. Babies with Paine syndrome, for example, may require a feeding tube due to difficulties or trouble swallowing. Unlike most infants, they may seem disinterested in the world around them.

Paine syndrome also produces specific problems related to movement. Infants affected by the disease develop spasticity. This nervous system disorder, in which muscles do not relax properly after being stretched, can cause muscle stiffness, pain, or physical deformity. It can also lead to repetitive spasms by a particular muscle or group of muscles (these spasms are known as myoclonic jerks). Aside from spasticity, an infant with Paine syndrome may experience generalized seizures.

Vision can also be affected, resulting in optic atrophy. This eye disorder causes a degeneration of the nerves carrying information from the eyes to the brain. Optic atrophy can lead to blurry vision or other visual disturbances.

The underlying cause of Paine syndrome, which is sometimes referred to as microcephaly-spastic diplegia syndrome, is unknown. The effects of the disease are thought to stem from the limited growth of the cerebellum and other areas of the brain. Autopsies of affected children have revealed underdevelopment of this region, as well as abnormalities in the cerebrum and other brain structures.

Paine syndrome is considered very similar to another genetic, congenital disease known as Seemanova syndrome. Both diseases have a number of symptoms in common, though Seemanova syndrome lacks certain characteristics of the former (such as an underdeveloped cerebellum). Some doctors view both conditions as variations of a more broadly defined disorder called Paine-Seemanova syndrome.

Genetic profile

The **gene** responsible for Paine syndrome has not been identified, but is believed to lie on the X chromosome. For this reason, the disease is referred to as an X-

KEY TERMS

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are "essential amino acids" which the body cannot make and must therefore be obtained from food).

Congenital—Refers to a disorder which is present at birth.

Gavage—Feeding tube.

Neurological—Relating to the brain and central nervous system.

linked genetic condition. Only males are affected. Females do not usually develop the symptoms of Paine syndrome but they may be carriers of the gene associated with the disease. This is because women have two X **chromosomes**, while men only possess one. Even if a woman possesses the gene for Paine syndrome on one of her X chromosomes, she still has a second X chromosome that is free of the faulty gene. This second X chromosome is what protects her from developing symptoms of Paine syndrome, though she may be able to transmit the disease to her children.

Demographics

Paine syndrome is a rare, congenital disease that only affects males. Most children born with it do not survive infancy.

Signs and symptoms

The most visible symptom of Paine syndrome is often the size of the head, which is smaller than normal. Affected infants may experience feeding difficulties or swallowing problems. They may not appear to be growing properly or may seem disinterested in their environment. The development of motor skills and speech is delayed.

In simple terms, Paine syndrome causes structural abnormalities in the cerebellum, cerebrum, and other parts of the brain. The skull itself is abnormally small, due to the fact that its size is dictated by brain growth. Damage to the optic nerve may also occur. In addition, Paine syndrome produces elevated amino acid levels in the urine and cerebrospinal fluid.

Diagnosis

The disease is often diagnosed at birth when the size of the head is measured, though a small head circumference may be identified later during a routine exam if it is not detected shortly after delivery. Imaging procedures (such as an x ray, CT scan, or MRI) are used to identify the structural abnormalities of the brain and skull. Analyses of blood and urine are also performed. An electroencephalogram (EEG), a non-invasive test that measures the electrical activity of the brain, may be recommended to help assess developmental problems or detect relevant brain or nervous system abnormalities.

Treatment and management

There is no cure for Paine syndrome. The changes in brain structure associated with the disease cannot be reversed. When possible, treatment focuses on alleviating symptoms. Anticonvulsants, for example, can be used to help control seizures; dextroamphetamine may also be prescribed to ease symptoms. In addition to drugs, orthopedic surgery is sometimes necessary. Family education and **genetic counseling** for parents is also recommended.

Prognosis

Due to its debilitating effects on the brain and nervous system, Paine syndrome is usually fatal within one year after birth.

Resources

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ORGANIZATIONS

U.S. National Library of Medicine. 8600 Rockville Pike, Bethesda, MD 20894.

WEBSITES

U.S. National Library of Medicine. <http://www.nlm.nih.gov>.

Greg Annussek

Pallister-Hall syndrome

Definition

Pallister-Hall syndrome is an extremely rare developmental disorder marked by a spectrum of features ranging from mild (extra fingers or toes or a non-cancerous malformation in the hypothalamus region of the brain) to severe (laryngotracheal cleft, an opening between the windpipe and voicebox that can be fatal in newborns).

Description

First reported in 1980 by American geneticist Judith G. Hall and American medical doctor Philip D. Pallister, Pallister-Hall syndrome is often diagnosed at birth. Some symptoms are immediately noticeable, including short limbs, extra digits, unusual facial features, or blockage of the anal opening. Some signs, such as mental retardation and abnormalities of the heart, lung, or kidneys, must be diagnosed by a physician.

Newborn infants with Pallister-Hall syndrome must be carefully watched for signs of hypopituitarism (insufficient production of growth hormones by the pituitary gland), which can cause fatal complications if not promptly treated. Similarly, inadequate activity of the adrenal gland can be lethal in newborns. If not immediately recognized, an imperfectly formed anus can also develop serious complications in a newborn. Because of its sometimes-serious consequences, Pallister-Hall syndrome is considered part of the CAVE (cerebro-acro-visceral early lethality) group of disorders.

This syndrome is also known by a variety of alternative names, including congenital hypothalamic hamartoblastoma, hamartopolydactyly syndrome, hypothalamic hamartoblastoma syndrome, Hall syndrome 2, hypothalamic hamartoblastoma-hyperphalangeal hypoendocrine-hypoplastic anus (4H) syndrome, hypothalamic hamartoblastoma-hypopituitarism-imperforate anus-postaxial polydactyly syndrome, microphallus-imperforate anus-syndactyly-hamartoblastoma-abnormal lung lobulation-polydactyly (MISHAP) syndrome, and renal-anal-lung-polydactyly-hamartoblastoma (RALPH) syndrome.

Genetic profile

Pallister-Hall syndrome is believed to have autosomal dominant **inheritance**, meaning that it can occur in either sex, and is passed from generation to generation when an abnormal **gene** is received from one parent and a normal gene is received from the other. Affected patients have a 50% chance of passing the disorder to each offspring. In most such cases, signs and symptoms in affected offspring are similar to those of the parents. However, Pallister-Hall syndrome is more commonly found in isolated cases involving individuals with no family history of the disorder. These cases are thought to result from new, random, genetic mutations with no known cause. The gene responsible is GL13 (chromosonal locus 7p13). Because of the rarity of this disorder and the subtlety of its identifying characteristics, the ratio of these random mutation cases to inherited cases is not known.

Demographics

As of early 2001, only about 100 cases of this very rare genetic disorder were known. Males are believed affected by Pallister-Hall syndrome about twice as often as females. The disorder is not limited to particular ethnic groups. Some researchers have proposed that many patients with Pallister-Hall signs and symptoms have been misdiagnosed as having a related genetic disorder, isolated post-axial polydactyly type A (PAP-A). It should be noted that Pallister-Hall has only been known since 1980, and that the syndrome's full spectrum is still being investigated. As this spectrum expands, greater numbers of milder cases are being uncovered.

Signs and symptoms

This disorder is noted for a wide range of signs and symptoms, including the following:

- Abnormalities of the head, neck, and facial areas including short neck, short midface, flat nasal bridge, small tongue, noticeable underdevelopment of one jaw compared to the other, asymmetric skull, cleft palate and other irregularities of the palate, cleft larynx or epiglottis, cysts on the gums, and ears that are small, low-set, and abnormally rotated toward the back of the head.
- Hypothalamic hamartoblastoma, a non-cancerous tumor in the hypothalamus. It grows at the same rate as nearby brain tissue, up to 4 cm across, taking the place of the hypothalamus. Most hypothalamic hamartomas have no symptoms, but in some cases they can cause neurological problems including gelastic **epilepsy**, which causes chest and diaphragm movements similar to those that occur during laughter.
- Inhibited flow of cerebrospinal fluid in the brain.
- Limb abnormalities including short limbs, extra fingers or toes (central or postaxial polydactyly), webbing of fingers or toes (syndactyly), abnormally small fingernails or toenails, or absent nails.

KEY TERMS

Adrenal gland—A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

Hypothalamus—A part of the forebrain that controls heartbeat, body temperature, thirst, hunger, body temperature and pressure, blood sugar levels, and other functions.

Pituitary gland—A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

- Respiratory abnormalities including underdeveloped or abnormally developed lungs
- Anus lacking the usual opening
- Congenital heart defects
- Kidneys with abnormal development or placement
- Underdeveloped or abnormally developed adrenal, pituitary, or thyroid glands. This can lead to decreased activity of these glands. Some Pallister-Hall newborns cannot survive due to insufficient activity of the adrenal gland. An underdeveloped pituitary gland can also have lethal consequences. Symptoms of hypopituitarism may include hypoglycemia, jaundice, or unusual drowsiness.
- In males, unusually small penis, underdeveloped testicles, or failure of one or both testes to descend normally
- Retarded growth in most patients
- Mild mental retardation
- Spinal abnormalities
- Dislocated hips
- Signs of puberty may appear unusually early

Diagnosis

Both clinical examination and family history are used to diagnose Pallister-Hall syndrome.

The hallmark clinical findings are hypothalamic hamartoma (a non-cancerous tumor in the hypothalamus), as well as extra fingers or toes. Another sign useful for diagnostic purposes is bifid epiglottis, a cleft in the thin flap of cartilage behind the base of the tongue. This particular malformation is almost never seen except in cases of Pallister-Hall syndrome. It rarely causes problems.

Prenatal testing may be conducted by ultrasound, however its effectiveness in detecting Pallister-Hall syndrome is not conclusive.

A molecular genetic test exists to scan the coding regions of the GL13 gene for mutations, but as of early 2001 such testing was available only for scientific research purposes.

Treatment and management

Management will depend on the specific signs and symptoms present.

Unless there are unusual complications, hamartoblastomas are usually left in place. However, it is sometimes necessary to surgically remove a hamartoblastoma when it causes undue pressure on the brain (**hydrocephalus**). Hamartoblastomas are usually monitored throughout the life of the patient. Typically, magnetic resonance imaging (MRI) is used, because hypothalamic hamartomas are sometimes not visible on computerized tomography (CT) scans or cranial ultrasound examinations.

Because of the dangers posed by adrenal insufficiency, Pallister-Hall patients will often be assessed for cortisol deficiency. Cortisol (hydrocortisone) is an important steroid hormone released by the adrenal glands. Patients are also likely to see an endocrinologist to evaluate their growth hormone, luteinizing hormone, follicle-stimulating hormone, and thyroid hormone levels. X rays may be taken of limbs, and the kidneys may be examined by ultrasound. The epiglottis may be examined by laryngoscope, an instrument used to view the larynx through the mouth.

If patients show evidence of aspiration (when breathing forces foreign matter into the lungs) they should be seen immediately by an ear, nose, and throat specialist to determine whether laryngotracheal cleft is present.

Newborns with hypopituitarism should immediately be given hormonal replacement therapy and watched closely for life-threatening complications.

A surgical procedure known as a colostomy may be needed to correct an imperforate anus.

Similarly, extra toes or fingers can be surgically corrected on an elective basis.

Seizures, such as those caused by gelastic epilepsy, may also require symptomatic treatment.

Whenever a new case of Pallister-Hall syndrome is uncovered, it is advisable to also examine the parents and any offspring for the disorder. Evaluation for a parent is likely to include a cranial MRI, x rays of hands and feet, and laryngoscopy.

At the time of writing in early 2001, the U.S. National Human Genome Research Institute was seeking to recruit between 50 and 100 Pallister-Hall patients for a comprehensive study of the severity, natural history, origins, and other aspects of the syndrome. Researchers there intend to investigate the relationship between Pallister-Hall and some disorders with similar characteristics, including **Greig cephalopolysyndactyly syndrome** (GCPS), **McKusick-Kaufman syndrome** (MKS), **Bardet-Biedl syndrome** (BBS), and oro-facial digital syndromes (OFDs). No special drugs or other treatments were to be used in this study.

Prognosis

Because of the broad range and severity of Pallister-Hall signs and symptoms, the prognosis varies widely from case to case.

In families in which multiple cases of Pallister-Hall syndrome exist, the prognosis for any new case is likely to be similar to the existing cases. Mild forms of the syndrome have been identified in a number of large, healthy families believed to have a normal life expectancy.

In cases that occur in isolated individuals, the prognosis is based on the specific abnormalities present. Reviews of these abnormalities as reported in scientific literature have limited usefulness because published cases tend to be more severe than those normally encountered. Unless there are life-threatening malformations such as hypopituitarism, the prognosis for these random cases is considered excellent.

There is a 50% chance that any child of a Pallister-Hall patient will be affected.

Resources

ORGANIZATIONS

Pallister-Hall Foundation. RFD Box 3000, Fairground Rd., Bradford, VT 05033.

Patient Recruitment and Public Liaison Office Building 61, 10 Cloister Court, Bethesda, Maryland 20892-4754 1 (800) 411-1222.

WEBSITES

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David L. Helwig

Pancreatic beta cell agenesis

Definition

Pancreatic beta cell agenesis is a rare disorder in which a child is born with no beta cells—the cells in the pancreas that produce insulin—resulting in diabetes.

Description

Diabetes mellitus is a disease caused by elevated blood sugar and can result in numerous medical problems that can affect the kidney, eyes, cardiovascular system, skin, and joints. There are two common types. Type 1 results from destruction of the insulin-producing cells (beta cells) of the pancreas and usually occurs in children of at least one year of age or young adults. Injected insulin is required to allow glucose (sugar) to enter the body's cells to be used for energy. Type 2 diabetes occurs mostly in older, often obese, adults and results from the body's cells' decreased ability to respond to the insulin the body produces. In contrast to these two types, neonatal diabetes is extremely rare. Neonatal diabetes is usually transient, meaning that it goes away after some time. It appears to be caused by immaturity of the beta cells; babies with this form of the disease usually recover and do not require insulin before about three months of age. Fewer than forty cases of permanent neonatal diabetes had been reported as of 2001. Reported causes of neonatal diabetes have included absence of the whole pancreas, absence of the clusters (called islets) that contain the beta cells, and absence of the beta cells themselves. This last form is known as pancreatic beta cell agenesis.

Only one confirmed case of pancreatic beta cell agenesis has been reported (1994). This was an infant girl who had a low birth weight and showed high glucose (sugar) in her blood during a routine test. She was also pale, with a low body temperature, rapid breathing and low muscle tone. Her health was further complicated by a diagnosis of an additional metabolic disorder, methylmalonic acidemia (MMA). She died at the age of 16 days. An autopsy showed that her pancreas had islets, which are the bundles of cells containing insulin-producing cells as well as cells that produce other hormones. However, the islets did not contain insulin-producing cells.

Genetic profile

Pancreatic beta cell agenesis may be an autosomal recessive disorder. This means that a child would have to inherit two abnormal copies of a specific **gene**, one from each parent, in order to have the disorder. The infant

KEY TERMS

Agenesis—Failure of an organ, tissue, or cell to develop or grow.

Beta cells—Specialized cells of the pancreas that make insulin.

Diabetes mellitus—The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Metabolic disorder—A disorder that affects the metabolism of the body.

Metabolism—The total combination of all the chemical processes that occur within cells and tissues of a living body.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

described above had both pancreatic beta cell agenesis and MMA, also known to be an autosomal recessive disorder. A gene causing MMA is located on chromosome 6, and studies of this child's genes and **chromosomes** showed that she inherited two identical copies of at least part of chromosome 6 from her father, a condition known as paternal uniparental isodisomy, instead of one copy of this region from each parent. The MMA was caused by the **inheritance** of two identical defective MMA genes from her father and the beta cell agenesis was then believed to have been caused by the inheritance of two abnormal copies of another gene. On other chromosomes, it has been shown that certain genes only work when they come from the mother and others only from the father. Several cases of transient neonatal diabetes have also had two identical copies of paternal chromosome 6 or other abnormalities of chromosome 6. This suggests that there may be a connection between pancreatic beta cell agenesis and transient neonatal diabetes. It is believed that the relevant region of chromosome 6 contains a gene that delays the production of insulin and only works when inherited from the father. As of 2001, there were no reports in the literature describing the status of the beta cells in infants with transient neonatal diabetes. Presumably, this is because a pancreatic biopsy would be required, and this procedure would be too strenuous for a fragile baby.

Demographics

The overall incidence of neonatal, or newborn, diabetes mellitus is approximately one in 400,000 to one in 600,000 live births, and many cases are transient, with the infants requiring insulin for an average of three months. These infants do appear to be at an increased risk of developing type 2 diabetes in young adulthood. As of 2001, fewer than 40 cases of well-documented permanent neonatal diabetes had been reported. Only two infants with neonatal diabetes had been demonstrated (by autopsy) to completely lack the insulin-producing cells in the pancreas at birth. One of these is described above and had both pancreatic beta cell agenesis and another disorder called methylmalonic acidemia. She also had low birth weight, typical of children with neonatal diabetes because of the inability to metabolize glucose. The second child was of normal birth weight, suggesting that she originally had beta cells that were subsequently destroyed, perhaps by an autoimmune process as in type 1 diabetes. Both of these infants died in the newborn period.

Signs and symptoms

Symptoms of neonatal diabetes include lethargy, dehydration, and breathing difficulties. In the laboratory, high levels of glucose (sugar) in the blood and urine are demonstrated. Children with neonatal diabetes, including the child with pancreatic beta cell agenesis, are generally of low birth weight.

Diagnosis

Neonatal diabetes, like other forms of diabetes, is diagnosed by high blood sugar levels. Permanent and transient forms of neonatal diabetes are indistinguishable at initial diagnosis. Determining if the cause of neonatal diabetes is pancreatic beta cell agenesis was done after death in the published cases by studying the pancreas from an autopsy; a pancreatic biopsy would be required to make this diagnosis in a living child.

Treatment and management

Pancreatic beta cell agenesis, like type 1 and some cases of type 2 diabetes mellitus, is treated by insulin injection.

Prognosis

Both children reported to have absence of beta cells were diagnosed on autopsy because they died at birth. The second child's prognosis was complicated by the fact that she had the additional MMA disorder. It is not

known as of 2001 if any living children have pancreatic beta cell agenesis.

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ORGANIZATIONS

American Diabetes Association. 1701 N. Beauregard St., Alexandria, VA 22311. (703) 549-1500 or (800) 342-2383. <http://www.diabetes.org>.

Juvenile Diabetes Foundation International (JDF). 120 Wall St., New York, NY 10005. (212) 785-9500 x708 or (800) 533-2873. <http://www.jdf.org>.

Toni I. Pollin, MS, CGC

Pancreatic cancer

Definition

The pancreas is a gland found in the abdomen behind the stomach. The pancreas secretes juice that breaks down fats and proteins and releases hormones, such as insulin, to control blood sugar levels. Pancreatic cancer is uncontrolled growth of cells of the pancreas. Spreading of cancer from the original site to other areas in the body is known as metastasis. A higher than average number of pancreatic cancer cases occurring in the same family is known as familial pancreatic cancer.

Description

Most pancreatic cancer grows from cells from the exocrine pancreas, the secreting portion of the pancreas. The most common appearance of pancreatic cancer cells is gland-like, which is termed "adenocarcinoma."

In most cases, it is difficult to determine the cause of the pancreatic cancer. Both environmental as well as genetic risk factors have been suggested for pancreatic cancer. A high fat diet has been linked to increased pancreatic cancer risk whereas diets high in vegetables and fruits seem to lower the risk. Smoking is known to increase the risk of pancreatic cancer. It is estimated that as many as 30% of pancreatic cancer cases are linked to smoking. Alcohol use and coffee consumption has been linked with increased pancreatic cancer risk, in some studies, but this connection has not been proven. Previous stomach surgery also may increase the risk of pancreatic cancer. Certain occupations such as farming or manufacturing may increase the risk of pancreatic cancer. The relationship of diabetes to pancreatic cancer has been closely studied. It is uncertain whether diabetes is the cause or the symptom of pancreatic cancer. Presence of diabetes; however, may alert health care providers to the presence of pancreatic cancer. Long-term inflammation of the pancreas, chronic pancreatitis, may increase the risk of pancreatic cancer, as well. Genetic risk factors have also been reported.

Genetic profile

Several studies have reported a higher rate of pancreatic cancer in relatives of individuals with the disease. Hereditary causes are estimated to account for about 10% of all pancreatic cancer. Some risk is thought to be due to known hereditary conditions whereas in other cases a known genetic syndrome has not been determined.

Known syndromes

There are several known genetic syndromes that increase the risk of pancreatic cancer. Alterations in the **gene**, BRCA2, have been clearly linked to increases in breast and **ovarian cancer** as well as a potential increased pancreatic cancer risk. **Hereditary pancreatitis**, which is due to alterations in the cationic trypsinogen gene on chromosome 7 at 7q35, causes long-term, recurrent inflammation of the pancreas. Individuals with hereditary pancreatitis are estimated to have a 40% risk of pancreatic cancer by age 70. Changes or "mutations" in the CDKN2A (*p16*) gene increase risks of melanoma, a type of skin cancer, and, possibly, pancreatic cancer. Hereditary Non-polyposis Colon Cancer (HNPCC) or Lynch syndrome, increases the risk of colon cancer and other cancers including pancreatic cancer, in some families. Peutz-Jeghers, **Familial adenomatous polyposis** (FAP), and **Li-Fraumeni syndromes** all cause relatively increased risks of pancreatic cancer in addition to the other symptoms of the disorders. All of these disorders are inherited in an autosomal dominant pattern. With autosomal dominant **inheritance**, men and women are equally likely to inherit the syndrome and children of affected individuals are at 50% risk of inheriting the gene alteration. Other syndromes, some with different inheritance patterns, may be linked to pancreatic cancer as well. **Genetic testing** is available for many of these known syndromes but, due to the complexity of the disorders, **genetic counseling** should be considered before testing.

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

BRCA2—Gene, when altered, known to cause increased risks of breast, ovarian and, possibly, pancreatic cancer.

Cationic trypsinogen gene—Gene known to cause hereditary pancreatitis when significantly altered.

CDKN2A* or *p16—Gene, when altered, known to cause Familial atypical multiple mole melanoma (FAMMM) syndrome and possibly increased pancreatic cancer risk.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Duct—Tube-like structure that carries secretions from glands.

Duodenum—Portion of the small intestine nearest the stomach; the first of three parts of the small intestine.

Endoscopic retrograde cholangiopancreatography (ERCP)—A method of viewing the pancreas by inserting a thin tube down the throat into the pancreatic and bile ducts, injection of dye and performing x rays.

Exocrine pancreas—The secreting part of the pancreas.

Familial adenomatous polyposis (FAP)—Inherited syndrome causing large numbers of polyps and increased risk of colon cancer and other cancers.

Fine needle aspiration (FNA)—Insertion of a thin needle through the skin to an area of sample tissue.

Hereditary non-polyposis colon cancer (HNPCC)—A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called Lynch syndrome.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Li-Fraumeni syndrome—Inherited syndrome known to cause increased risk of different cancers, most notably sarcomas.

Melanoma—Tumor, usually of the skin.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Palliative—Treatment done for relief of symptoms rather than a cure.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Pancreatitis—Inflammation of the pancreas.

Peutz-Jeghers syndrome—Inherited syndrome causing polyps of the digestive tract and spots on the mouth as well as increased risk of cancer.

Radiation—High energy rays used in cancer treatment to kill or shrink cancer cells.

Staging—A method of describing the degree and location of cancer.

Whipple procedure—Surgical removal of the pancreas and surrounding areas including a portion of the small intestine, the duodenum.

Familial pancreatic cancer

Some families with increased pancreatic cancer rates do not have a known genetic syndrome as the cause. It is possible that environmental factors or chance could explain some cases of pancreatic cancer in families; however, it is also possible that other as yet unknown genetic causes could explain some cases of familial pancreatic cancer. While genetic testing may not be available in some cases, some families do participate in collections or "registries" of familial pancreatic cancer cases for research purposes.

Demographics

Pancreatic cancer is the fifth leading cause of cancer-related death for both men and women in the United States. Pancreatic cancer is more common in industrialized countries, with African Americans in the United States having one of the highest rates. The rate of pan-

creatic cancer increases with age, with most patients diagnosed between the ages of 60 and 80. Pancreatic cancer is more common in men than in women.

Signs and symptoms

Since the symptoms of pancreatic cancer are not specific to the disease, and typically do not develop until the cancer has progressed, it is difficult to diagnosis pancreatic cancer at an early stage. The symptoms of pancreatic cancer can include:

- weight loss
- loss of appetite
- abdominal or back pain
- jaundice (yellow color to skin and eyes)
- digestive problems including greasy stool
- sudden diabetes

Diagnosis

If pancreatic cancer is suspected, regardless of the cause, a physical exam often is done first and then certain body imaging tests may be recommended. One imaging test that may be done is a computed tomography (CT) scan. This exam creates pictures of the interior of the body from computer-analyzed differences in x rays passing through the body. Evidence of substantial tumors or any metastasis can be detected by CT scanning. Sometimes, CT is used to assist with sampling of tissue, a biopsy. There are different types of biopsies. One type of biopsy is performed by inserting a thin needle through the skin into a suspicious area (called fine needle aspiration or FNA) and a sample of tissue is removed. Once a biopsy is taken, the tissue is examined for evidence of cancer and this typically determines the diagnosis. Ultrasound is another method of viewing internal body structures. In ultrasound, sound waves are passed into the body. Since tissues bounce sound waves differently, a computer is able to develop an image based on the returned sound waves. Ultrasound is generally less expensive and more easily available than CT; however, there are limitations to the use of ultrasound in viewing the pancreas. So, ultrasound may be used in addition to CT. Endoscopic retrograde cholangiopancreatography (ERCP) is a method of viewing the pancreas by inserting a thin tube down the throat, injecting of dye into the pancreatic and bile ducts and then x rays are taken.

Once the tumor and any metastasis has been identified and the biopsy tissue evaluation has been done, the tumor can be "staged." Staging is a ranking system that provides a method of describing the extent and characteristics of a cancer. There are different staging systems. One simple staging system ranks cancers from 0 to IV with IV being the most advanced cancer. Staging can be used to help determine the treatment and prognosis for a given cancer.

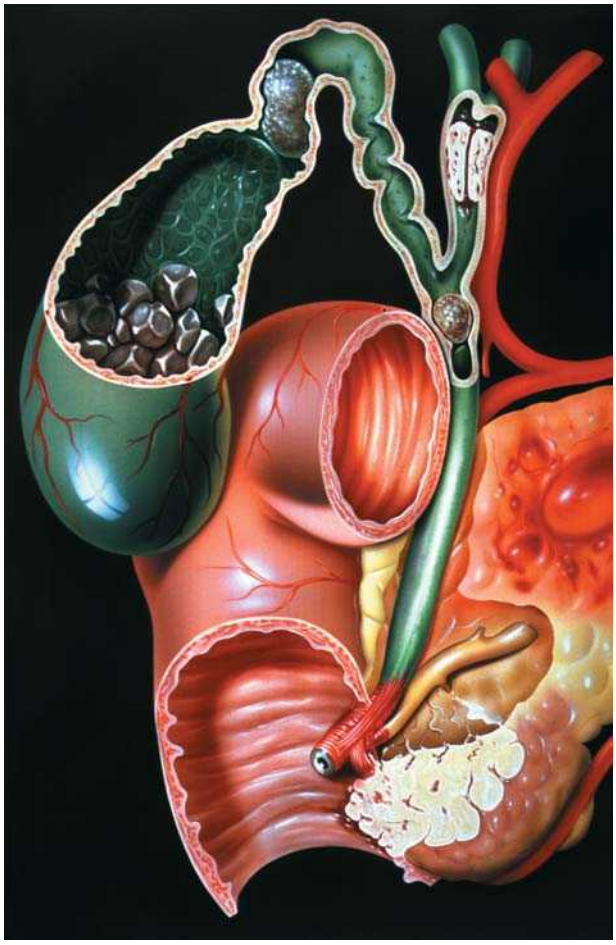


Illustration of invading cancer of the human pancreas. The gallbladder and gallstones at top right of image are green, and the pink c-shaped tube at left and center are the duodenum. *(Custom Medical Stock Photo, Inc.)*

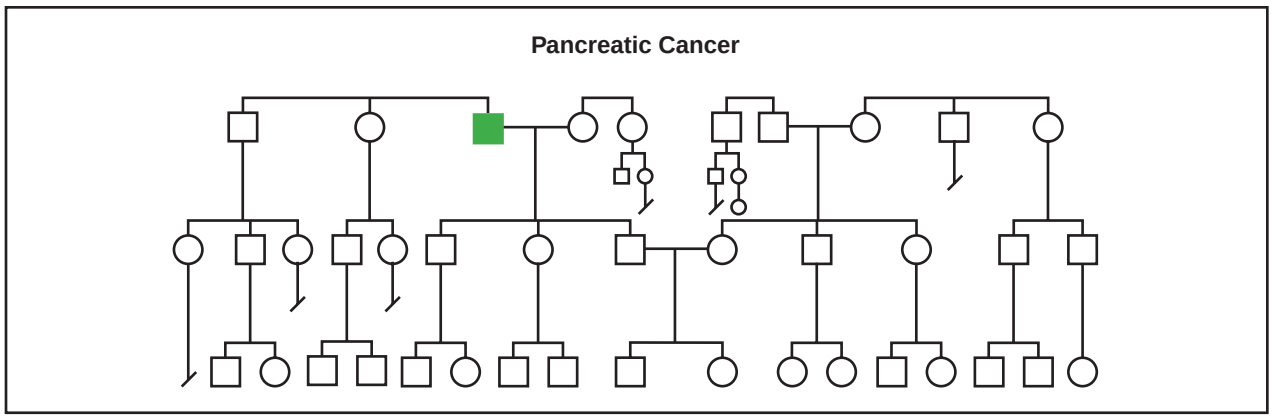
Treatment and management

Surgery

While surgery oftens provides the best chance of a cure, frequently, it is not possible due to the spread of cancer. Removal of all or part of the pancreas and other areas such as the duodenum (the first part of the small intestine) is known as the Whipple procedure. Complications of this surgery include infection and bleeding.

Chemotherapy

Cancer-killing medicine, chemotherapy, has been found to increase survival in some patients. This medi-



(Gale Group)

cine can be given intravenously or by mouth. Once in the bloodstream, chemotherapy agents reach other parts of the body. There are different chemotherapy agents and the side effects may be different as well. Side effects may include nausea, hair loss, low blood counts, and other effects.

Radiation therapy

Recent improvements in radiation, high-energy rays directed at cancer cells, have made this therapy more effective. Although cures due to radiation therapy are uncommon, relief from pain and increased survival are possible. Side effects of radiation therapy may include skin changes, upset stomach, and other effects.

Palliative treatment

Sometimes, surgery, radiation, or other therapies are done to relieve symptoms rather than cure the cancer. This is known as palliative treatment.

Clinical trials

Involvement in research as part of clinical trials may be offered to certain patients. Although treatments through clinical trials may not be proven, it is an opportunity to potentially benefit from new therapies.

Screening

Screening before cancer development may be considered for patients with a higher risk of the disease either due to a known genetic syndrome or a family history of pancreatic cancer. ERCP and ultrasound has been used for screening purposes; however, the usefulness and cost-effectiveness of these tests for screening needs evaluation. Surveillance may be considered for persons with two or more close relatives (first degree relatives) with pancreatic cancer or one close relative (first degree) with pancreatic cancer at an early age (before age 50) or two or more distant relatives (second degree) with one affected before age 50. Prophylactic pancreatectomy, surgical removal of the pancreas before any cancer development, has been considered in cases with a hereditary risk. The concern with prophylactic pancreatectomy is that there is a risk of serious complications and so the decision must be weighed carefully.

Prognosis

It is difficult to diagnose pancreatic cancer early and so, frequently, the cancer has spread to other locations in the body such as the liver or lymph nodes (part of the immune system). Survival rates five years after pancreatic cancer, in general, have been reported to be between 3% and 25%. Most long-term survivors originally had smaller tumors and no spreading of the cancer. Of course, every case of pancreatic cancer is different and it is difficult to predict the course and survival for each individual patient. The prognosis of individuals with hereditary risk factors is dependent on the syndrome, if any, and the aggressiveness of the particular cancer.

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National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda, MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

National Familial Pancreas Tumor Registry. Johns Hopkins Hospital, Weinberg Building, Room 2242, 401 North Broadway, Baltimore, MD 21231-2410. (410) 955-9132. <http://www.path.jhu.edu/pancreas>.

WEBSITES

Pancreatic Action Network (PanCan). <http://www.pancan.org>.

Kristin Baker Niendorf, MS, CGC

Pancreatic carcinoma *see* **Pancreatic cancer**

Panic disorder

Definition

A panic disorder is a psychological state characterized by acute (rapid onset) feelings, which engulf a person with a deep sense of destruction, death, and imminent doom. The main feature of panic disorder (PD) is a history of previous panic attacks (PA). The PA symptoms are pronounced and the affected person will gasp for air, have increased breathing (hyperventilate), feel dizzy (light headed), and develop a loss of sensation (parasthesia). Most patients will run outside and symptoms like increased breathing will slow and the PA symptoms will subside. Most PA last three to ten minutes. It is rare for PA to extend in duration over 30 minutes.

Description

The essential characteristics of panic disorder consist of specific and common criteria. The affected person usually has recurrent and unexpected panic attacks (the active presentation of panic disorder). The PA is characterized by a discrete, rapid onset feeling of intense fear or discomfort. Affected persons have several somatic (referring to physical signs) or cognitive (thinking) symptoms. Affected persons usually react in a manner that indicates impending doom. They commonly exhibit signs of a sweating, racing heart beat, chest pain, shortness of breath, and the perception of feeling smothered. The panic attack (PA) is usually followed by one month (or more) of one or more of the following thought processes:

- Persistent concern or preoccupation about having future attacks
- Worry about the possible consequences, complications, or behavioral changes associated with attacks (e.g. losing control, going crazy, or having a serious medical condition like a heart attack).

Genetic profile

Panic disorder definitely runs in families and twin studies suggest that about 20% of patients who have the criteria for diagnosis have first-degree relatives with the disorder. In families with no history of affected first-degree relatives the prevalence decreases to 4%. The ratio between monozygotic twins (identical) twins to dizygotic (non-identical) twins is 5:1 for PD. Recent evidence suggests that there is a genetic mutation in the SLC6A4 **gene**. This gene is related to a brain chemical called serotonin, a chemical in the brain, which is known to effect mood. If the transport of serotonin is imbalanced, then certain parts of the brain may not receive the correct stimulus causing alterations in mood. Some studies have demonstrated that there is no positive family history in about 50% of patients diagnosed with PD. Other possible causes of PD include social learning and autonomic responsivity (the attack will affect the body and hypersensitizes nerve cells in the brain).

Demographics

PD usually begins during the affected persons late teens or in the twenties, and is uncommon after age 35 and unusual after age 45 years. Global studies suggest that the lifetime prevalence of PD is between 1.5% and 3.5%. In the United States approximately 3–5% of the population are affected with the disorder. In any given year approximately 1.7% of the U.S. population has PD. This represents about 2.4 million Americans. PD is twice as common in females compared to males (female:male ratio is 2:1).

Agoraphobia (anxiety state about being in situations or places that might make escape embarrassing or difficult) is seen in approximately one-third to one-half of persons who meet the criteria for PD diagnosis. Other reports indicate that about 95% of persons affected with agoraphobia also have a previous history or current diagnosis of PD. In some cultures PA is believed to be associated with magic or witchcraft. Additional causes of PA may include intentional suppression of one's freedoms or public life.

Signs and symptoms

Criteria for panic attack:

1. Cardiac palpitations (pounding, racing, or accelerated heart rate).
2. Sweating.

3. Shaking (trembling).
4. Breathing difficulties, including shortness of breath or perceptions of being smothered.
5. Feeling of choking.
6. Chest discomfort or pain.
7. Feeling light-headed (faint, dizzy or unsteady).
8. Stomach discomfort or nausea.
9. Affected individuals may lose contact with reality during the attack.
10. A feeling of being detached and out of contact with oneself.
11. Fear of losing control of oneself (going "crazy").
12. Fear of dying.
13. Tingling or numbness sensations.

Criteria for panic disorder:

1. Recurrent and unexpected PA.
2. Worry about the consequences, implications, or behavioral changes associated with PA (perceptions of going "crazy," losing control of actions, or suffering from a life threatening condition, such as a heart attack).
3. PA is not caused by or associated with a medical condition.
4. PA is not associated with another mental disorder, such as phobia (an exaggerated fear to something like spiders or heights). Exposure to a specific phobia situation or object can promote a PA.

Criteria for agoraphobia:

1. The essential feature of agoraphobia is anxiety about being in situations or places that make escape embarrassing or difficult. These fears usually involve characteristic clusters of situations that include being on a bridge, being in a crowd, standing in line in a department store, or traveling in a train, bus, or automobile. Elevators are another common cause promoting the occurrence of PA. These situations, which lead to the PA, are often difficult or embarrassing to abruptly flee from.
2. Avoidance of the affected person's fear, which usually limits travel away from home, causing impaired functioning.

Criteria for PD without agoraphobia:

Recurrent unexpected PA. At least one attack followed by one month or more of one or more of the following symptoms:

- Persistent concern about having future attacks
- Worry about consequences associated with attacks
- A change in behavioral patterns related to the attacks (e.g. the affected person avoids travel).
- Absence of agoraphobia
- PA are not due to a medical condition
- PA not associated with another mental disorder (e.g. phobias).

Criteria for panic disorder with agoraphobia:

1. Criteria 1, 2, and 5 for PD without agoraphobia must be present.
2. The presence of agoraphobia.

Diagnosis

There are no specific laboratory findings associated with diagnosing PD. However, evidence suggests that some affected persons may have low levels of carbon dioxide and an important ion in the human body called bicarbonate (helps in regulating blood from becoming to acidic or alkaline). These chemical changes may hypersensitize (making cells excessively sensitive) nerve cells, which can increase the activity of other structures throughout the body, such as sweat glands (sweating) and the heart (racing, accelerated or pounding rate). Additionally, lactic acid (a chemical made in the body from sugar) plays a role in nerve cell hypersensivity. The diagnosis of PD can be made accurately if the specific symptoms and criteria are established.

Neuroimaging studies indicate that the arteries (vessels that deliver oxygen rich blood to cells and tissues) are constricted (smaller diameter) as a result of increased breathing rates during a PA.

The consulting clinician must exclude other possible causes of panic attacks such as intoxication with stimulant drugs (cocaine, caffeine, amphetamines [speed]). Withdrawal from alcohol and barbiturates can also induce panic-like behaviors. Additionally, the consulting therapist should obtain a comprehensive medical history and examination to determine if the PA is caused by a medical condition frequently observed in hormonal diseases (overactive thyroid), tumors that secrete chemicals causing a person to have pronounced "hyper" changes (racing heartbeat, sweating, shaking). Other causes include a possible cardiac (heart) disease such as an irregularly beating heart.

Treatment and management

Moderate to severe PD is characterized by frequent PA ranging from five to seven times a week or with sig-

nificant disability associated with anxiety between episodes. In addition to cognitive-behavioral therapy an affected person will usually require medications. There are three classes of medications commonly prescribed for PD patients.

Tricyclic antidepressants

Tricyclic antidepressants are a class of medications used to treat **depression** and other closely related mental disorders. Individuals affected with PD are usually given imipramine, which has been shown in some studies to be effective in approximately 70% of cases. Medications in this category usually have a prolonged lag time until a positive response is observed. This is primarily due to adverse side effects, which prevent rapid increases of dosage and also because they act on specific chemical imbalances in the brain, which take time to stabilize.

The first choice of medication treatment for PD is tricyclics (imipramine, desipramine, and nortriptyline). These medications require careful dosing and monitoring. The actual blood level (therapeutic level necessary to make improvements) may vary in special populations who have the disorder. Elderly patients may require a smaller dose, due to decrease in metabolism (in this context metabolism refers to the breakdown of large chemicals to smaller ones for usage) and kidney function, which are part of aging. Some patients may develop gastrointestinal (stomach) side effects, which may interfere with absorption from the gut, thereby decreasing beneficial blood levels. Furthermore, patients who receive tricyclics may develop dry mouth and low blood pressure. The heart may be adversely affected (altered rate and rhythm) especially in patients with preexisting diseases, causing direct damage or strain in the heart. Affected persons receiving tricyclics also commonly experience changes in sexual functioning, including loss of desire and ejaculation. Adverse (negative) side effects usually decrease patient compliance (the person stops taking medications to avoid side effects). Recently, a new group of tricyclics was made available. These tricyclics (fluoxetine, sertraline, paroxetine and fluvoxamine) act on specific areas in the brain to correct potential chemical imbalances.

Monoamine oxidase inhibitors (MAOIs)

A second line category of medications used to treat PD are the monoamine oxidase (a chemical that assists in storing certain chemicals in nerve cells) inhibitors (MAOI). MAOI will stop the action of MAO, thereby decreasing the amount of certain chemicals in the brain that may influence PAs. This group of medications is effective in approximately 75–80% of cases, especially for refractory (not active) depression. Affected individuals using MAOI must avoid specific foods to prevent a hypertensive crisis (when the blood pressure rapidly increases). These foods include cheeses (except cream cheese, cottage cheese, and fresh yogurt); liver of all types; meat and yeast extracts; fermented or aged meats (such as salami and bologna); broad and Chinese bean pods; all types of alcohol-containing products; soy sauce; shrimp and shrimp paste; and sauerkraut. Although MAOI are effective medications for treatment of PD, they are underutilized due to strict dietary limitations.

KEY TERMS

Palpitation—An irregular heartbeat.

Phobia—An exaggerated fear.

Recurrent—Tendency to repeat.

Benzodiazepines

Benzodiazepines are another class of medications used to treat PD. They include medications such as diazepam (Valium), lorazepam, and clonazepam. They have been reported to be effective in 70–90% of patients with PD. However, the effective dose is approximately two to three times higher for PD than milder forms of simple anxiety (these medications are usually indicated for mild anxiety). This increased dosing in PD patients is undesirable since there is risk of physical dependence and withdrawal (commonly exhibited when the medication is rapidly tapered down or stopped). However, they are indicated when PD affected patients respond poorly to tricyclics or have a fear of taking MAOIs due to dietary restrictions and problems associated with eating the wrong foods accidentally.

Long term management

Reassuring the patient with PD that anticipated panic attacks are unlikely while taking medication is essential for long-term maintenance. Cognitive-behavioral therapy is also important for long-term treatment. Weaning off medications must be done slowly since patients develop a sense of security that they will not have an attack while actively dosing.

Prognosis

The course of PD and agoraphobia varies considerably over time. Some cases may experience spontaneous remissions (the disorder is present but it is not active). The course can be so variable that an affected person may go on for years without a PA, then have several attacks,

and then enter a second phase of remission, which may last for years. In some cases a decrease in PA may be closely related to a decrease and avoidance of anxiety-associated situations, which promote agoraphobia. Agoraphobia itself may become chronic (long term or permanent) with or without PA. In general, approximately 50–60% will recover substantially five to 20 years after the initial attack. Approximately 20% will still have long term impairment, which will stay the same or slightly worsen. Generally, the earlier treatment is sought, the better the outcome. The course in children and adolescents is chronic (long term), usually lasting about three years. Generally, PD shows the highest risk of developing new psychological disorders during follow up visits. If PA is treated early, anticipatory anxiety and phobia may be more manageable and responsive to treatment.

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ORGANIZATIONS

Anxiety Disorders Association of America. 11900 Parklawn Dr., Suite 100, Rockville, MD 20852. (301) 231-9350. Fax: (301) 231-7392. anxdis@adaa.org.

Laith Farid Gulli, MD
Bilal Nasser, MS

Parkinson disease

Definition

Parkinson disease (PD) is a progressive movement disorder marked by tremors, rigidity, slow movements (bradykinesia), and posture instability. It occurs when cells in one of the movement-control centers of the brain begin to die for unknown reasons. PD was first noted by British physician James Parkinson in the early 1800s.

Description

Usually beginning in a person's late fifties or early sixties, Parkinson disease causes a progressive decline in movement control, affecting the ability to control initiation, speed, and smoothness of motion. Symptoms of PD are seen in up to 15% of those ages 65–74, and almost 30% of those ages 75–84.

Genetic profile

Most cases of PD are sporadic. This means that there is a spontaneous and permanent change in nucleotide sequences (the building blocks of genes). Sporadic mutations also involve unknown environmental factors in combination with genetic abnormalities. The abnormal **gene** (mutated gene) will form an altered end-product or protein. This will cause abnormalities in specific areas in the body where the protein is used. Some evidence suggests that the disease is transmitted by autosomal dominant **inheritance**. This implies that an affected parent has a 50% chance of transmitting the disease to any child. This type of inheritance is not commonly observed. The most recent evidence is linking PD with a gene that codes for a protein called alpha-synuclein. Further research is attempting to fully understand the relationship with this protein and nerve cell degeneration.

Demographics

PD affects approximately 500,000 people in the United States, both men and women, with as many as 50,000 new cases each year.

Signs and symptoms

The immediate cause of PD is degeneration of brain cells in the area known as the substantia nigra, one of the movement control centers of the brain. Damage to this area leads to the cluster of symptoms known as "parkinsonism." In PD, degenerating brain cells contain Lewy bodies, which help identify the disease. The cell death leading to parkinsonism may be caused by a number of conditions, including infection, trauma, and poisoning. Some drugs given for psychosis, such as haloperidol (Haldol) or chlorpromazine (thorazine), may cause parkinsonism. When no cause for nigral cell degeneration can be found, the disorder is called idiopathic parkinsonism, or Parkinson disease. Parkinsonism may be seen in

other degenerative conditions, known as the "parkinsonism plus" syndromes, such as progressive supranuclear palsy.

The substantia nigra, or "black substance," is one of the principal movement control centers in the brain. By releasing the neurotransmitter known as dopamine, it helps to refine movement patterns throughout the body. The dopamine released by nerve cells of substantia nigra stimulates another brain region, the corpus striatum. Without enough dopamine, the corpus striatum cannot control its targets, and so on down the line. Ultimately, the movement patterns of walking, writing, reaching for objects, and other basic actions cannot function properly, resulting in the symptoms of parkinsonism.

There are some known toxins that can cause parkinsonism, most notoriously a chemical called MPTP, found as an impurity in some illegal drugs. Parkinsonian symptoms appear within hours of ingestion, and are permanent. MPTP may exert its effects through generation of toxic molecular fragments called free radicals, and reducing free radicals has been a target of several experimental treatments for PD using antioxidants.

It is possible that early exposure to some as-yet-unidentified environmental toxin or virus leads to undetected nigral cell death, and PD then manifests as normal age-related decline brings the number of functioning nigral cells below the threshold needed for normal movement. It is also possible that, for genetic reasons, some people are simply born with fewer cells in their substantia nigra than others, and they develop PD as a consequence of normal decline.

KEY TERMS

AADC inhibitors—Drugs that block the amino acid decarboxylase; one type of enzyme that breaks down dopamine. Also called DC inhibitors, they include carbidopa and benserazide.

Akinesia—A loss of the ability to move; freezing in place.

Bradykinesia—Extremely slow movement.

COMT inhibitors—Drugs that block catechol-O-methyltransferase, an enzyme that breaks down dopamine. COMT inhibitors include entacapone and tolcapone.

Dopamine—A neurochemical made in the brain that is involved in many brain activities, including movement and emotion.

Dyskinesia—Impaired ability to make voluntary movements.

MAO-B inhibitors—Inhibitors of the enzyme monoamine oxidase B. MAO-B helps break down dopamine; inhibiting it prolongs the action of dopamine in the brain. Selegiline is an MAO-B inhibitor.

Orthostatic hypotension—A sudden decrease in blood pressure upon sitting up or standing. May be a side effect of several types of drugs.

Substantia nigra—One of the movement control centers of the brain.

Symptoms

The identifying symptoms of PD include:

- Tremors, usually beginning in the hands, often occuring on one side before the other. The classic tremor of PD is called a "pill-rolling tremor," because the movement resembles rolling a pill between the thumb and forefinger. This tremor occurs at a frequency of about three per second.
- Slow movements (bradykinesia) occur, which may involve slowing down or stopping in the middle of familiar tasks such as walking, eating, or shaving. This may include freezing in place during movements (akinesia).
- Muscle rigidity or stiffness, occuring with jerky movements replacing smooth motion.
- Postural instability or balance difficulty occurs. This may lead to a rapid, shuffling gait (festination) to prevent falling.
- In most cases, there is a "masked face," with little facial expression and decreased eye-blinking.

In addition, a wide range of other symptoms may often be seen, some beginning earlier than others:

- Depression
- Speech changes, including rapid speech without inflection changes
- Problems with sleep, including restlessness and nightmares
- Emotional changes, including fear, irritability, and insecurity
- Incontinence
- Constipation
- Handwriting changes, with letters becoming smaller across the page (micrographia)
- Progressive problems with intellectual function (**dementia**)

Diagnosis

The diagnosis of Parkinson disease involves a careful medical history and a neurological exam to look for characteristic symptoms. There are no definitive tests for PD, although a variety of lab tests may be done to rule out other causes of symptoms, especially if only some of the identifying symptoms are present. Tests for other causes of parkinsonism may include brain scans, blood tests, lumbar puncture, and x rays.

Treatment and management

There is no cure for Parkinson disease. Most drugs treat the symptoms of the disease only, although one drug, selegiline (Eldepryl), may slow degeneration of the substantia nigra.

Exercise, nutrition, and physical therapy

Regular, moderate exercise has been shown to improve motor function without an increase in medication for a person with PD. Exercise helps maintain range of motion in stiff muscles, improve circulation, and stimulate appetite. An exercise program designed by a physical therapist has the best chance of meeting the specific needs of the person with PD. A physical therapist may also suggest strategies for balance compensation and techniques to stimulate movement during slowdowns or freezes.

Good nutrition is important to maintenance of general health. A person with PD may lose some interest in food, especially if depressed, and may have nausea from the disease or from medications, especially those known as dopamine agonists. Slow movements may make it difficult to eat quickly, and delayed gastric emptying may lead to a feeling of fullness without having eaten much. Increasing fiber in the diet can improve constipation, soft foods can reduce the amount of needed chewing, and a prokinetic drug such as cisapride (Propulsid) can increase the movement of food through the digestive system.

People with PD may need to limit the amount of protein in their diets. The main drug used to treat PD, L-dopa, is an amino acid, and is absorbed by the digestive system by the same transporters that pick up other amino acids broken down from proteins in the diet. Limiting protein, under the direction of the physician or a nutritionist, can improve the absorption of L-dopa.

No evidence indicates that vitamin or mineral supplements can have any effect on the disease other than in the improvement of the patient's general health. No antioxidants used to date have shown promise as a treatment except for selegiline, an MAO-B inhibitor. A large, carefully controlled study of vitamin E demonstrated that it could not halt disease progression.

Drugs

The pharmacological treatment of Parkinson disease is complex. While there are a large number of drugs that can be effective, their effectiveness varies with the patient, disease progression, and the length of time the drug has been used. Dose-related side effects may preclude using the most effective dose, or require the introduction of a new drug to counteract them. There are five classes of drugs currently used to treat PD.

DRUGS THAT REPLACE DOPAMINE One drug that helps replace dopamine, levodopa (L-dopa), is the single most effective treatment for the symptoms of PD. L-dopa is a derivative of dopamine, and is converted into dopamine by the brain. It may be started when symptoms begin, or when they become serious enough to interfere with work or daily living.

L-dopa therapy usually remains effective for five years or longer. Following this, many patients develop motor fluctuations, including peak-dose "dyskinesias" (abnormal movements such as tics, twisting, or restlessness), rapid loss of response after dosing (known as the "on-off" phenomenon), and unpredictable drug response. Higher doses are usually tried, but may lead to an increase in dyskinesias. In addition, side effects of L-dopa include nausea and vomiting, and low blood pressure upon standing (orthostatic hypotension), which can cause dizziness. These effects usually lessen after several weeks of therapy.

ENZYME INHIBITORS Dopamine is broken down by several enzyme systems in the brain and elsewhere in the body; blocking these enzymes is a key strategy to prolonging the effect of dopamine. The two most commonly prescribed forms of L-dopa contain a drug to inhibit the amino acid decarboxylase (an AADC inhibitor), one type of enzyme that breaks down dopamine. These combination drugs are Sinemet (L-dopa plus carbidopa) and Madopar (L-dopa plus benzaseride). Controlled-release formulations also aid in prolonging the effective interval of an L-dopa dose.

The enzyme monoamine oxidase B (MAO-B) inhibitor selegiline may be given as add-on therapy for L-dopa. Research indicates selegiline may have a neuroprotective effect, sparing nigral cells from damage by free radicals. Because of this, and the fact that it has few side effects, it is also frequently prescribed early in the disease before L-dopa is begun. Entacapone and tolcapone, two inhibitors of another enzyme system called catechol-O-methyltransferase (COMT), may soon reach the market

as early studies suggest that they effectively treat PD symptoms with fewer motor fluctuations and decreased daily L-dopa requirements.

DOPAMINE AGONISTS Dopamine works by stimulating receptors on the surface of corpus striatum cells. Drugs that also stimulate these cells are called dopamine agonists, or DAs. DAs may be used before L-dopa therapy, or added on to avoid requirements for higher L-dopa doses late in the disease. DAs available in the United States as of early 1998, include bromocriptine (Permax, Parlodel), pergolide (Permax), and pramipexole (Mirapex). Two more, cabergoline (Dostinex) and ropinirole (Requip), are expected to be approved soon. Other dopamine agonists in use outside the United States include lisuride (Dopergine) and apomorphine. Side effects of all the DAs are similar to those of dopamine, plus confusion and hallucinations at higher doses.

ANTICHOLINERGIC DRUGS Anticholinergics maintain dopamine balance as levels decrease. However, the side effects of anticholinergics (dry mouth, constipation, confusion, and blurred vision) are usually too severe in older patients or in patients with dementia. In addition, anticholinergics rarely work for very long. They are often prescribed for younger patients who have predominant shaking. Trihexyphenidyl (Artane) is the drug most commonly prescribed.

DRUGS WHOSE MODE OF ACTION IS UNCERTAIN Amantadine (Symmetrel) is sometimes used as an early therapy before L-dopa is begun, and as an add-on later in the disease. Its anti-parkinsonian effects are mild and not seen in many patients. Clozapine (Clozaril) is effective especially against psychiatric symptoms of late PD, including psychosis and hallucinations.

Surgery

Two surgical procedures are used for treatment of PD that cannot be controlled adequately with drug therapy. In PD, a brain structure called the globus pallidus (GPi) receives excess stimulation from the corpus striatum. In a pallidotomy, the GPi is destroyed by heat, delivered by long thin needles inserted under anesthesia. Electrical stimulation of the GPi is another way to reduce its action. In this procedure, fine electrodes are inserted to deliver the stimulation, which may be adjusted or turned off as the response dictates. Other regions of the brain may also be stimulated by electrodes inserted elsewhere. In most patients, these procedures lead to significant improvement for some motor symptoms, including peak-dose dyskinesias. This allows the patient to receive more L-dopa, since these dyskinesias are usually what cause an upper limit on the L-dopa dose.

A third procedure, transplant of fetal nigral cells, is still highly experimental. Its benefits to date have been modest, although improvements in technique and patient selection are likely to change that.

Alternative treatment

Currently, the best treatments for PD involve the use of conventional drugs such as levodopa. Alternative therapies, including acupuncture, massage, and yoga, can help relieve some symptoms of the disease and loosen tight muscles. Alternative practitioners have also applied herbal and dietary therapies, including amino acid supplementation, antioxidant (vitamins A, C, E, selenium, and zinc) therapy, B vitamin supplementation, and calcium and magnesium supplementation, to the treatment of PD. Anyone using these therapies in conjunction with conventional drugs should check with their doctor to avoid the possibility of adverse interactions. For example, vitamin B_6 (either as a supplement or from foods such as whole grains, bananas, beef, fish, liver, and potatoes) can interfere with the action of L-dopa when the drug is taken without carbidopa.

Prognosis

Despite medical treatment, the symptoms of Parkinson disease worsen over time, and become less responsive to drug therapy. Late-stage psychiatric symptoms are often the most troubling, including difficulty sleeping, nightmares, intellectual impairment (dementia), hallucinations, and loss of contact with reality (psychosis).

Prevention

There is no known way to prevent Parkinson disease.

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Parkinson Disease Foundation. 710 West 168th St. New York, NY 10032. (800) 457-6676. <http://www.apdaparkinson.com>.

Worldwide Education and Awareness for Movement Disorders (WE MOVE). Mt. Sinai Medical Center, 1 Gustave Levy Place, New York, NY 10029. (800) 437-MOV2. <http://www.wemove.org>.

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Laith Farid Gulli, MD

Parkinson disease-juvenile *see* **Parkinson disease**

Parkinsonism *see* **Parkinson disease**

Paroxysmal nocturnal hemoglobinuria

Definition

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired disease in which the bone marrow produces abnormal blood cells, including red blood cells. Such red blood cells are too easily broken, and the hemoglobin inside them is released. The disease is sometimes characterized by nighttime attacks (nocturnal paroxysms) on red blood cells, when the cells break down and spill hemoglobin into the urine (hemoglobinuria). The result is reddish-brown urine upon rising in the morning.

Description

Also known as Marchiafava-Micheli syndrome, PNH was first identified in 1882. PNH is caused by a change (mutation) in a **gene** that prevents it from making a fat required by the three types of blood cells: red blood cells, white blood cells, and platelets.

When the fat (glycosylphosphatidylinositol, or GPI) is missing from the outside walls of blood cells, proteins cannot stick to the cells and the cells cannot function normally. In healthy red blood cells, GPI binds proteins that protect the cells from chemical attack. In healthy white blood cells, GPI may attach to proteins that help the cells fight infections. In healthy platelets, GPI helps control the platelets clotting mechanism.

Not only are all types of blood cells abnormal in PNH, but the numbers of blood cells are decreased. The decrease in red blood cells, coupled with their destruction, causes anemia in people affected with PNH.

The severity of PNH varies greatly from individual to individual. In some affected people, blood in the urine is barely detectable; others lose so much blood that they require repeated transfusions to stay alive. In severe cases, abnormal platelets may cause abnormal clotting, and about one-third of people with PNH die from clots in the veins of the liver, stomach, or brain.

Genetic profile

Mutations in any of 10 different genes can affect the production of GPI. Only one gene, however, is always altered in PNH. This is the PIG-A gene, located on the X chromosome. Females have two X **chromosomes** (only one is active) and males have one X chromosome.

People are not born with an altered PIG-A gene, probably because such an abnormality would be lethal to an unborn child. Rather, changes occur in the PIG-A gene sometime after birth, resulting in PNH. PNH is thus an acquired genetic disease, not an inherited disease.

Demographics

PNH is a rare disease. In a million people, only about two to six cases of PNH will be diagnosed. PNH is most common in adults between the ages of 30 and 50, although it has been identified in infants less than one year old and people as old as 82. The disease is slightly more common in females than in males (the ratio is 1.2-to-1). Researchers have not reported that the disease is more common in one population than others, although Asians are much less likely to have clotting problems than are Caucasians.

Signs and symptoms

Only about one-quarter of people with PNH have the telltale sign, reddish-brown urine, for which the disease is named. Other symptoms vary greatly among affected individuals. All those affected, however, have some degree of red cell breakdown that results in more or less severe anemia.

Contributing to anemia in people with PNH is the decreased production of red blood cells in the center of the bones (bone marrow). When the needed fat, GPI, is missing, the bone marrow fails to produce functioning red blood cells, white blood cells, and platelets, and the numbers of these blood cells drop dangerously low. This condition is called bone marrow failure.

Those affected with PNH may have frequent infections because their white blood cells are decreased in number and the cells that circulate in the blood are abnormal. Individuals with PNH may have stomach pain because abnormal platelets can cause clotting in liver and

stomach veins. Headaches may result when clots form in veins that pass through the brain.

Diagnosis

PNH and other types of blood diseases are usually diagnosed by examining a sample of bone marrow cells or tissue under a microscope for abnormalities. Doctors obtain the sample by performing a bone marrow aspiration or biopsy on the individual. In PNH, the bone marrow usually looks empty because so few blood cells are being produced.

Two tests that are more specific to PNH require the affected person's blood. The Ham test, developed in 1938, has long been the standard laboratory test for confirming PNH. The test determines whether an individual's red blood cells break down when attacked by certain chemicals. The Ham test is very sensitive and identifies minuscule levels of abnormal red blood cells, but it also identifies individuals with another disease of the red blood cells, congenital dyserythropoietic anemia. A second laboratory test, the sugar water test, works on principles similar to the Ham test. Although the sugar water test is less sensitive to low levels of abnormal red blood cells than the Ham test, it is positive only when the person has PNH.

The most sensitive and specific laboratory test for PNH is flow cytometry. In this test, the individual's blood cells are treated with a chemical that normally binds to proteins on the cell wall. The size of the treated cells is measured to determine if the chemical is attached to the cell. In people with PNH, there are no proteins on the cell wall so the chemical does not bind and the cells appear smaller than normal cells.

Treatment and management

PNH can be treated with a bone marrow transplant, a procedure in which the diseased bone marrow is destroyed and replaced with healthy bone marrow. The operation can be risky, however, so bone marrow transplants are most often performed on children. The operation is most successful if the healthy bone marrow is donated by an identical twin of the affected child, but bone marrow from other family members can sometimes be used.

If a suitable bone marrow donor cannot be found or if the affected person is not strong enough to withstand a bone marrow transplant, PNH can be managed by supportive treatment. Those affected may take drugs to prevent clots from forming and to prevent red blood cells from breaking down. If the number of blood cells falls dangerously low, affected individuals may receive multiple transfusions of blood cells or may be given drugs. When a person has lost a lot of red blood cells, doctors may prescribe iron supplements to help build up the blood again.

Gene therapy is an experimental treatment for PNH. In gene therapy, the normal PIG-A gene is inserted into the affected person's cells, where it takes the place of the abnormal gene and begins making the missing fat. The effectiveness of gene therapy for PNH has not yet been proven in humans.

Prognosis

After an affected individual has been diagnosed with PNH, he or she usually lives for another 10 to 20 years. About 25% of people with PNH live more than 25 years after first being diagnosed. In a few people (about 15%), the disease disappears altogether and the person recovers spontaneously.

Most people who die from PNH do so because of abnormal clotting. About 10% of these individuals develop and eventually die from another disease involving red blood cells, aplastic anemia. About 5% of people with PNH develop a disease involving abnormal white blood cells, acute myelogenous leukemia.

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Glycosylphosphatidylinositol (GPI)—A fat that attaches proteins to the outside walls of blood cells.

Hemoglobin—Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

Red blood cell—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

White blood cell—A cell in the blood that helps fight infections.

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ORGANIZATIONS

Anemia Institute for Research and Education. 151 Bloor St. West, Suite 600, Toronto, ONT M5S 1S4. Canada (877) 99-ANEMIA. <http://www.anemiainstitute.net>.

Aplastic Anemia Foundation. PO Box 613, Annapolis, MD 21404-0613. (800) 747-2820. <http://www.aplastic.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paroxysmal Nocturnal Hemoglobinuria (PNH) Support Group. <http://www.thegrid.net/asmaltz/Support%20Group.htm>.

Linnea E. Wahl, MS

Partial 11q monosomy syndrome *see* **Jacobsen syndrome**

Patau syndrome

Definition

Patau syndrome, also called trisomy 13, is a congenital (present at birth) disorder associated with the presence of an extra copy of chromosome 13. The extra chromosome 13 causes numerous physical and mental abnormalities, especially heart defects. Patau syndrome is named for Dr. Klaus Patau, who reported the syndrome and its association with trisomy in 1960.

Description

Children normally inherit 23 **chromosomes** from each parent, for a total of 46 chromosomes. A typical human being has 46 chromosomes: 22 pairs of non-sex linked chromosomes and one pair of sex-linked chromosomes that determine the child's sex. Sometimes a child may end up with more than 46 chromosomes because of problems with the father's sperm or the mother's egg; or, because of mutations that occurred after the sperm and the egg fused to form the embryo (conception).

Normally, there are two copies of each of the 23 chromosomes: one from each parent. A condition called trisomy occurs when three, instead of two, copies of a chromosome are present in a developing human embryo. An extra copy of a particular chromosome can come either from the egg or sperm, or because of mutations that occur after conception.

The most well-known trisomy-related disorder is **Down syndrome** (trisomy 21), in which the developing embryo has an extra copy of chromosome 21. Patau syndrome is trisomy 13, in which the developing embryo has three copies of chromosome 13.

An extra copy of chromosome 13 is not the only cause of Patau syndrome. Other changes in chromosome 13, such as mispositioning (translocation), can also result in the characteristics classified as Patau syndrome. In these cases, an error occurs that causes a portion of chromosome 13 to be exchanged for a portion of another chromosome. There is no production of extra chromosomes; but a portion of each affected chromosome is "misplaced" (translocated) to another chromosome.

Patau syndrome causes serious physical and mental abnormalities including heart defects; incomplete brain development; unusual facial features such as a sloping forehead, a smaller than average head (microcephaly), small or missing eyes, low set ears, and cleft palate or hare lip; extra fingers and toes (polydactyly); abnormal genitalia; spinal abnormalities; seizures; gastrointestinal hernias, particularly at the navel (**omphalocele**); and mental retardation. Due to the severity of these conditions, fewer than 20% of those affected with Patau syndrome survive beyond infancy.

Genetic profile

When an extra copy (trisomy) of a chromosome is made, it may either be a total trisomy (in which an extra copy of the entire chromosome is made), or partial trisomy (in which only one part of the chromosome is made an extra time).

In most cases of trisomy, errors in chromosome duplication occur at conception because of problems with the egg or the sperm that are coming together to produce an offspring. In these cases, every cell in the body of the offspring has an extra copy of the affected chromosome. However, errors in chromosome duplication may also occur during the rapid cell division that takes place immediately after conception. In these cases,

only some cells of the body have the extra chromosome error. The condition in which only some of the cells in the body have the extra chromosome is called mosaicism.

Seventy-five to 80% of the cases of Patau syndrome are caused by a trisomy of chromosome 13. Some of these cases are the result of a total trisomy, while others are the result of a partial trisomy. Partial trisomy generally causes less severe physical symptoms than full trisomy. Ten percent of these cases are of the mosaic type, in which only some of the body's cells have the extra chromosome. The physical symptoms of the mosaic form of Patau syndrome depends on the number and type of cells that carry the trisomy.

Most cases of trisomy are not passed on from one generation to the next. Usually they result from a malfunction in the cell division (mitosis) that occurs after conception. At least 75% of the cases of Patau syndrome are caused by errors in chromosome replication that occur after conception. The remaining 25% are caused by the **inheritance** of translocations of chromosome 13 with other chromosomes within the parental chromosomes. In these cases, a portion of another chromosome switches places with a portion of chromosome 13. This leads to errors in the genes on both chromosome 13 and the chromosome from which the translocated portion originated.

Demographics

Patau syndrome occurs in approximately one in 10,000 live births. In many cases, miscarriage occurs and the fetus does not survive to term. In other cases, the affected individual is stillborn. As appears to be the case in all trisomies, the risks of Patau syndrome seem to increase with the mother's age, particularly if she is over 30 when pregnant. Male and female children are equally affected, and the syndrome occurs in all races.

Signs and symptoms

The severity and symptoms of Patau syndrome vary with the type of chromosomal anomaly, from extremely serious conditions to nearly normal appearance and functioning. Full trisomy 13, which is present in the majority of the cases, results in the most severe and numerous internal and external abnormalities. Commonly, the forebrain fails to divide into lobes or hemispheres (**holoprosencephaly**) and the entire head is unusually small (microcephaly). The spinal cord may protrude through an opening in the vertebrae of the spinal column (myelomeningocele). Children who survive infancy have profound mental retardation and may experience seizures.

KEY TERMS

Aminocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

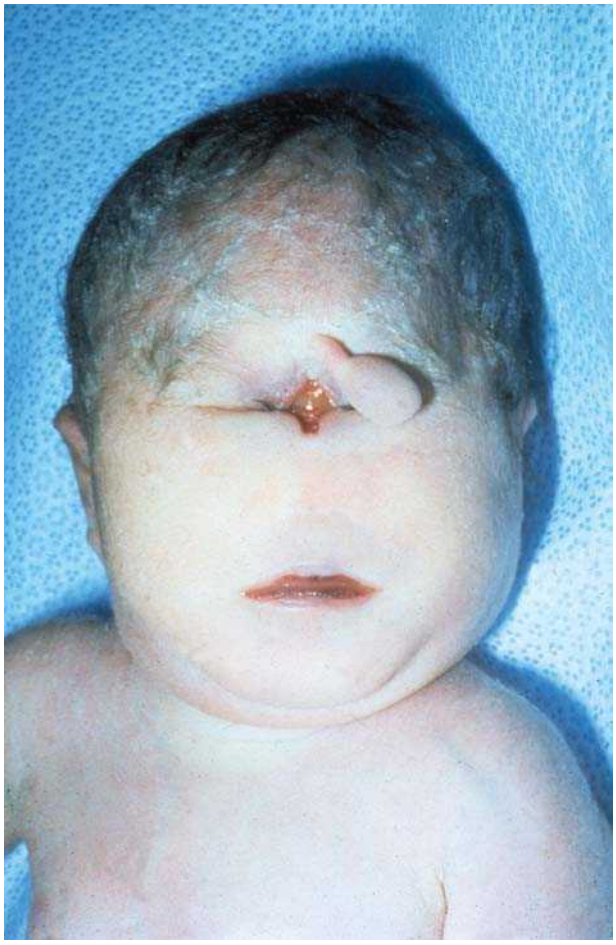
Karyotyping—A laboratory procedure in which chromosomes are separated from cells, stained, and arranged so that their structure can be studied under the microscope.

Mosaicism—A genetic condition resulting from a mutation, crossing over, or nondisjunction of chromosomes during cell division, causing a variation in the number of chromosomes in the cells.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.



A severe complication that may result in infants with Patau syndrome is synopthamia, in which the eyes are fused together in the center of the face. *(Photo Researchers, Inc.)*

Incomplete development of the optic (sight) and olfactory (smell) nerves often accompany the brain abnormalities described above. The eyes may be unusually small (microphthalmia) or one eye may be absent (anophthalmia). The eyes are sometimes set close together (hypotelorism) or even fused into a single structure. Incomplete development of any structures in the eye (**coloboma**) or failure of the retina to develop properly (retinal **dysplasia**) will also produce vision problems. Individuals with Patau syndrome may be born either partially or totally deaf and many are subject to recurring ear infections.

The facial features of many individuals with Patau syndrome appear flattened. The ears are generally malformed and low-set. Frequently, a child with trisomy 13 has a cleft lip, a cleft palate, or both. Other physical characteristics include loose folds of skin at the back of the neck, extra fingers or toes (polydactyly), permanently flexed (closed) fingers (camptodactyly), noticeably prominent heels, "rocker-bottom foot," and missing ribs. Genital malformations are common in individuals affected with Patau syndrome and include undescended testicles (cryptorchidism), an abnormally developed scrotum, and ambiguous genitalia in males, or an abnormally formed uterus (bicornuate uterus) in females.

In nearly all cases, affected infants have respiratory difficulties and heart defects, including atrial and ventricular septal defects (holes between chambers of the heart); malformed ducts that cause abnormal direction of blood flow (**patent ductus arteriosus**); holes in the valves of the lungs and the heart (pulmonary and aortic valves); and misplacement of the heart in the right, rather than the left side of the chest (dextrocardia). The kidneys and gastrointestinal system may also be affected with cysts similar to those seen in **polycystic kidney disease**. These abnormalities are frequently severe and life-threatening.

Partial trisomy of the distal segment of chromosome 13 generally results in less severe, but still serious, symptoms and a distinctive facial appearance including a short upturned nose, a longer than usual area between the nose and upper lip (philtrum), bushy eyebrows, and tumors made up of blood capillaries on the forehead (frontal capillary hemangiomata). Partial trisomy of the proximal segment of chromosome 13 is much less likely to be fatal and has been associated with a variety of facial features including a large nose, a short upper lip, and a receding jaw. Both forms of partial trisomy also result in severe mental retardation.

Beyond one month of age, other symptoms that are seen in individuals with Patau syndrome are: feeding difficulties and constipation, reflux disease, slow growth rates, curvature of the spine (**scoliosis**), irritability, sensitivity to sunlight, low muscle tone, high blood pressure, sinus infections, urinary tract infections, and ear and eye infections.

Diagnosis

Patau syndrome is detectable during pregnancy through the use of ultrasound imaging, **amniocentesis**, and chorionic villus sampling (CVS). At birth, the newborn's numerous malformations indicate a possible chromosomal abnormality. Trisomy 13 is confirmed by examining the infant's chromosomal pattern through karyotyping or another procedure. Karyotyping involves the separation and isolation of the chromosomes present in cells taken from an individual. These cells are generally extracted from cells found in a blood sample. The 22 non-sex linked chromosomes are identified by size, from largest to smallest, as chromosomes 1 through 22. The sex determining chromosomes are

also identified. Patau syndrome is confirmed by the presence of three, rather than the normal two, copies of chromosome 13.

Treatment and management

Some infants born with Patau syndrome have severe and incurable birth defects. However, children with better prognoses require medical treatment to correct structural abnormalities and associated complications. For feeding problems, special formulas, positions, and techniques may be used. Tube feeding or the placement of a gastric tube (gastrostomy) may be required. Structural abnormalities such as cleft lip and cleft palate can be corrected through surgery. Special diets, hearing aids, and vision aids can be used to mitigate the symptoms of Patau syndrome. Physical therapy, speech therapy, and other types of developmental therapy will help the child reach his or her potential.

Since the translocation form of Patau syndrome is genetically transmitted, **genetic counseling** for the parents should be part of the management of the disease.

Prognosis

Approximately 45% of infants with trisomy 13 die within their first month of life; up to 70% in the first six months; and over 70% by one year of age. Survival to adulthood is very rare. Only one adult is known to have survived to age 33.

Most survivors have profound mental and physical disabilities; however, the capacity for learning in children with Patau syndrome varies from patient to patient. Older children may be able to walk with or without a walker. They may also be able to understand words and phrases, follow simple commands, use a few words or signs, and recognize and interact with others.

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Support Organization for Trisomy 18, 13, and Related Disorders (SOFT). 2982 South Union St., Rochester, NY 14624. (800) 716-SOFT. <http://www.trisomy.org>.

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Paul A. Johnson

Patent ductus arteriosus

Definition

Patent ductus arteriosus (PDA) is a heart abnormality that occurs when the ductus arteriosus (the temporary fetal blood vessel that connects the aorta and the pulmonary artery) does not close at birth.

Description

The ductus arteriosus is a temporary fetal blood vessel that connects the aorta and the pulmonary artery before birth. The ductus arteriosus should be present and open before birth while the fetus is developing in the uterus. Since oxygen and nutrients are received from the placenta and the umbilical cord instead of the lungs, the ductus arteriosus acts as a "short cut" that allows blood to bypass the deflated lungs and go straight out to the body. After birth, when the lungs are needed to add oxygen to the blood, the ductus arteriosus normally closes. The closure of the ductus arteriosus ensures that blood goes to the lungs to pick up oxygen before going out to the body. Closure of the ductus arteriosus usually occurs at birth as levels of certain chemicals, called prostagladins, change and the lungs fill with air. If the ductus arteriosus closes correctly, the blood pumped from the heart goes to the lungs, back into the heart, and then out to the body through the aorta. The blood returning from the lungs and moving out of the aorta carries oxygen to the cells of the body.

KEY TERMS

Aorta—The main artery located above the heart which pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

Catheterization—The process of inserting a hollow tube into a body cavity or blood vessel.

Ductus arteriosus—The temporary channel or blood vessel between the aorta and pulmonary artery in the fetus.

Echocardiograph—A record of the internal structures of the heart obtained from beams of ultrasonic waves directed through the wall of the chest.

Electrocardiogram (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Endocarditis—A dangerous infection of the heart valves caused by certain bacteria.

Oxygenated blood—Blood carrying oxygen through the body.

Pulmonary artery—An artery that carries blood from the heart to the lungs.

Pulmonary edema—A problem caused when fluid backs up into the veins of the lungs. Increased pressure in these veins forces fluid out of the vein and into the air spaces (alveoli). This interferes with the exchange of oxygen and carbon dioxide in the alveoli.

In some infants, the ductus arteriosus remains open (or patent) and the resulting heart defect is known as patent ductus arteriosus (PDA). In most cases, a small PDA does not result in physical symptoms. If the PDA is larger, health complications may occur.

In an average individual's body, the power of blood being pumped by the heart and other forces leads to a certain level of pressure between the heart and lungs. The pressure between the heart and lungs of an individual affected by PDA causes some of the oxygenated blood that should go out to the body (through the aorta) to return back through the PDA into the pulmonary artery. The pulmonary artery takes the blood immediately back to the lungs. The recycling of the already oxygenated blood forces the heart to work harder as it tries to supply enough oxygenated blood to the body. In this case, the left side of the heart usually grows larger as it works harder and must contain all of the extra blood moving back into the heart. This is known as a left-to-right or aortic-pulmonary shunt.

As noted, the size of the PDA determines how much harder the heart has to work and how much bigger the heart becomes. If the PDA is large, the bottom left side of the heart is forced to pump twice as much blood because it must supply enough blood to recycle back to the lungs and move out to the body. As the heart responds to the increased demands for more oxygenated blood by pumping harder, the pulmonary artery has to change in size and shape in order to adapt to the increased amount and force of the blood. In some cases, the increase in size and shape changes the pressure in the pulmonary artery and lungs. If the pressure in the lungs is higher than that of the heart and body, blood returning to the heart will take the short cut back into the aorta from the pulmonary artery through the PDA instead of going to the lungs. This backward flowing of blood does not carry much oxygen. If blood without much oxygen is being delivered to the body, the legs and toes will turn blue or cyanotic. This is called a shunt reversal.

When a PDA results in a large amount of blood being cycled in the wrong order, either through a left-to-right shunt or shunt reversal, the overworked, enlarged heart may stop working (congestive heart failure) and the lungs can become filled with too much fluid (pulmonary edema). At this time, there is also an increased risk for a bacterial infection that can inflame the lining of the heart (endocarditis). These three complications are very serious.

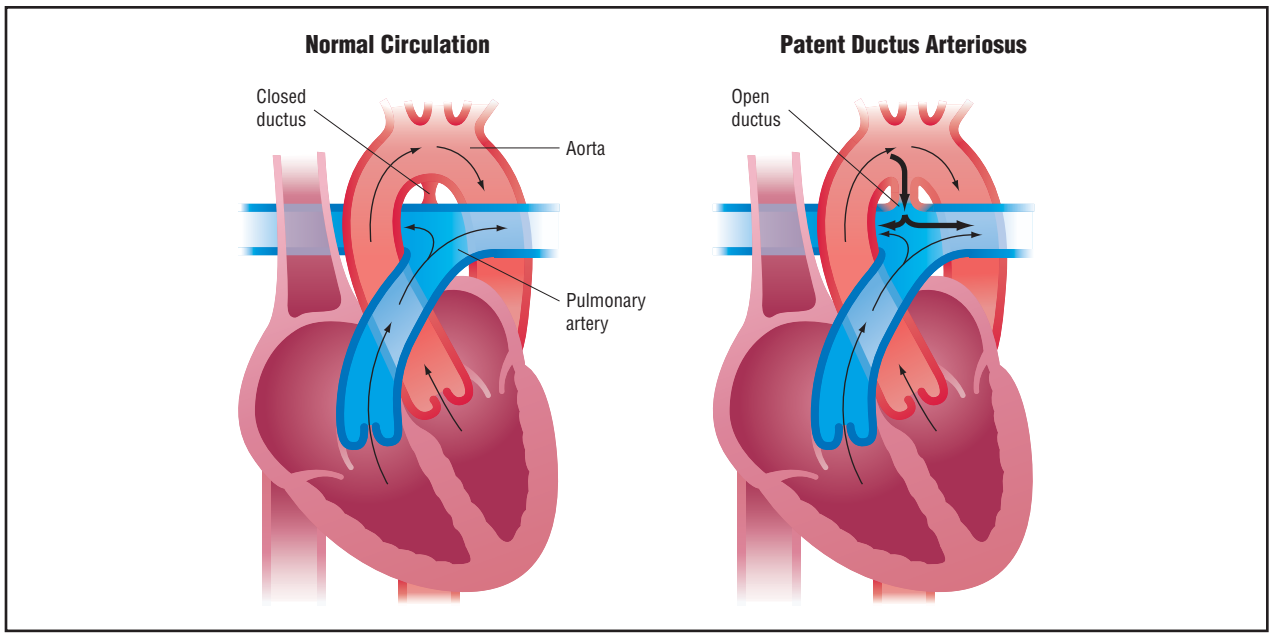
Genetic profile

PDA can be a result of an environmental exposure before birth, inheriting a specific changed or mutated **gene** or genes, a symptom of a genetic syndrome, or be caused by a combination of genetic and environmental factors (multifactorial).

Environmental exposures that can increase the chance for a baby to be affected by PDA include fetal exposure to rubella before birth, preterm delivery, and birth at a high altitude location.

PDA can be an inherited condition running in families as isolated PDA or part of a genetic syndrome. In either case, there are specific gene changes or mutations that lead to an abnormality in the elastic tissue forming the walls of the ductus arteriosus. The genes causing isolated PDA have not been identified, but it is known that PDA can be inherited through a family in an autosomal dominant pattern or an autosomal recessive pattern.

Every person has approximately 30,000 genes, which tell our bodies how to grow and develop correctly. Each gene is present in pairs since one is inherited from



Failure of the temporary fetal blood vessel that connects the aorta and the pulmonary artery (ductus arteriosus) to close after birth results in patent ductus arteriosus. This open duct interferes with proper blood flow through the aorta. *(Gale Group)*

the mother, and one is inherited from the father. In an autosomal dominant condition, only one changed or mutated copy of the gene for PDA is necessary for a person to have PDA. If a parent has an autosomal dominant form of PDA, there is a 50% chance for each child to have the same or similar condition.

PDA can also be inherited in an autosomal recessive manner. A recessive condition occurs when a child receives two changed or mutated copies of the gene for a particular condition, such as PDA (one copy from each parent). Individuals with a single changed or mutated copy of a gene for a recessive condition, are known as carriers, and have no health problems related to the condition. In fact, each person carries between five and 10 genes for harmful, recessive conditions. However, when two people who each carry a changed or mutated copy of the same gene for a recessive condition meet, there is a chance, with each pregnancy, for the child to inherit the two changed or mutated copies from each parent. In this case, the child would have PDA. For two known carriers, there is a 25% risk with each child to have a child with PDA, a 50% chance to have a child who is a carrier, and a 25% chance to have a child who is neither affected nor a carrier.

Most cases of PDA occur as the result of **multifactorial inheritance**, which is caused by the combination of genetic factors and environmental factors. The combined factors lead to isolated abnormalities in the elastic tissue forming the walls of the ductus arteriosus. Family studies can provide different recurrence risks depending on the family member affected by multifactorial PDA. If an individual is affected by isolated, multifactorial PDA, they have a 2–4% chance of having a child affected by PDA. If a couple has one child with isolated, multifactorial PDA, there is a 3% chance that another of their children could be affected by PDA. If a couple has two children affected by isolated, multifactorial PDA, there is a 10-25% chance that they could have another child affected by PDA.

Unless a specific pattern of **inheritance**, preterm delivery, or known exposure is found through the examination of a detailed pregnancy and family history, the multifactorial family studies are used to estimated the possible risk of recurrence of PDA in a family.

Demographics

PDA is a very common heart disorder. Though an exact incidence of PDA is difficult to determine, one review in 1990 found that approximately 8% of live births were found to be affected by PDA. PDA can occur in full-term infants, but is seen most frequently in preterm infants, infants born at a high altitude, and babies whose mothers were affected by German measles (rubella) during pregnancy. PDA is two to three times more common in females than males. PDA occurs in individuals of every ethnic origin and does not occur more frequently in any one country or ethnic population.

Signs and symptoms

The main sign of PDA is a constant heart murmur that sounds like the hum of a refrigerator or other machinery. This murmur is usually heard by the doctor using a stethoscope. Otherwise, there are no specific symptoms of PDA, unless the ductus arteriosus size is large. Children and adults with a large ductus arteriosus can show difficulty in breathing during moderate physical exercise, an enlarged heart, and failure to gain weight. In some cases, heart failure and pulmonary congestion can indicate a PDA.

Diagnosis

Diagnosis is most often made by detecting the characteristic "machinery" heart murmur heard by a doctor through a stethoscope. Tests such as a chest x ray, echocardiograph, and ECG are used to support the initial diagnosis. Other indications of PDA include failure to gain weight, frequent chest infections, heavy breathing during mild physical exertion, congestive heart failure, and pulmonary edema. Prenatal ultrasounds are unable to detect PDA because the heart defect does not occur until the time of birth.

Treatment and management

The treatment and management of PDA depends upon the size of the PDA and symptoms being experienced by the affected individual. In some cases, a PDA can correct itself in the first months of life. In preterm infants experiencing symptoms, the first step in correcting a PDA is treatment through medications such as indomethacin. In preterm infants whose PDA is not closed through medication, full term infants affected by PDA, and adults, surgery is an option for closing the ductus arteriosus. In 2000 and 2001, researchers have developed and reviewed alternatives to surgical closure such as interventional cardiac catheterization and video-assisted thorascopic surgical repair. A cardiologist can help individuals determine the best method for treatment based on their physical symptoms and medical history.

Prognosis

Adults and children can survive with a small opening remaining in the ductus arteriosus. Treatment, including surgery, of a larger PDA is usually successful and frequently occurs without complications. Proper treatment allows children and adults to lead normal lives.

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Kids with Heart. 1578 Careful Dr., Green Bay, WI 54304. (800) 538-5390. <http://www.execpc.com/~kdswhrt>.

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Dawn A. Jacob, MS

PC deficiency *see* **Pyruvate carboxylase deficiency with lactic acidemia**

Pedigree analysis

Definition

A pedigree is a family tree or chart made of symbols and lines that represent a patient's genetic family history. The pedigree is a visual tool for documenting biological relationships in families and the presence of diseases. Pedigree analysis is an assessment made by a medical professional about genetic risk in a family.

Purpose

Pedigrees are most often constructed by medical geneticists or genetic counselors. People are referred to genetic professionals because of concern about the presence of a genetic condition in a family member. Pedigree analysis can help identify a genetic condition running through a family, aids in making a diagnosis, and aids in determining who in the family is at risk for genetic conditions. During pedigree construction, the family's beliefs about the cause for a genetic disease or emotional issues related to a diagnosis may be revealed. For

instance, family members may experience guilt or shame about passing on a genetic trait. Thus, the communication process involved in taking the family history may allow the health care provider to identify areas in which the patient may need reassurance, education, or emotional support.

Creating a pedigree

Pedigree symbols

A standard set of symbols has been established for use in creating pedigrees. Some of the most commonly used symbols are shown in this entry. When a person is affected with a birth disorder, mental retardation, or other health problems, the individual is shaded or marked. If more than one condition is present in a family, different identifying marks should be made. A key to decipher these markings should also be included on the pedigree. The meaning of each horizontal and vertical line is also shown.

Information obtained

A typical pedigree is made of information about three generations of a family. The consultand is the person seeking genetic evaluation, counseling, or testing. The proband in a family is the person in a family affected with a genetic disorder. Beginning with the consultand, questions should be asked about the health of first, second, and third degree relatives. First-degree relatives are children, parents, and siblings. Second-degree relatives are half siblings, nieces, nephews, aunts and uncles, grandparents, and grandchildren. Third-degree relatives are first cousins. Important information to obtain on both sides of the family includes:

- ages or dates of birth
- presence of any birth disorders, learning problems, chronic illnesses, surgeries, or medical treatments
- presence of specific features of a disease if the condition is suspected in the family
- genetic testing results if previously performed in the family
- cause of death for deceased family members
- pregnancy losses, stillbirths, or infant deaths and causes
- infertility in the family
- ethnic background of the families
- consanguinity

It is important to establish the accuracy of information given by patients. Therefore, medical records are often requested in order to provide accurate risk assessment.

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Consanguinity—A mating between two people who are related to one another by blood.

Dizygotic twins—Non-identical twins that usually occur when two sperm fertilize two separate eggs during the same time period.

Obligate carrier—An individual who, based on pedigree analysis, must carry a genetic mutation for a particular genetic disease. Parents of a child with an autosomal recessive disorder are obligate carriers.

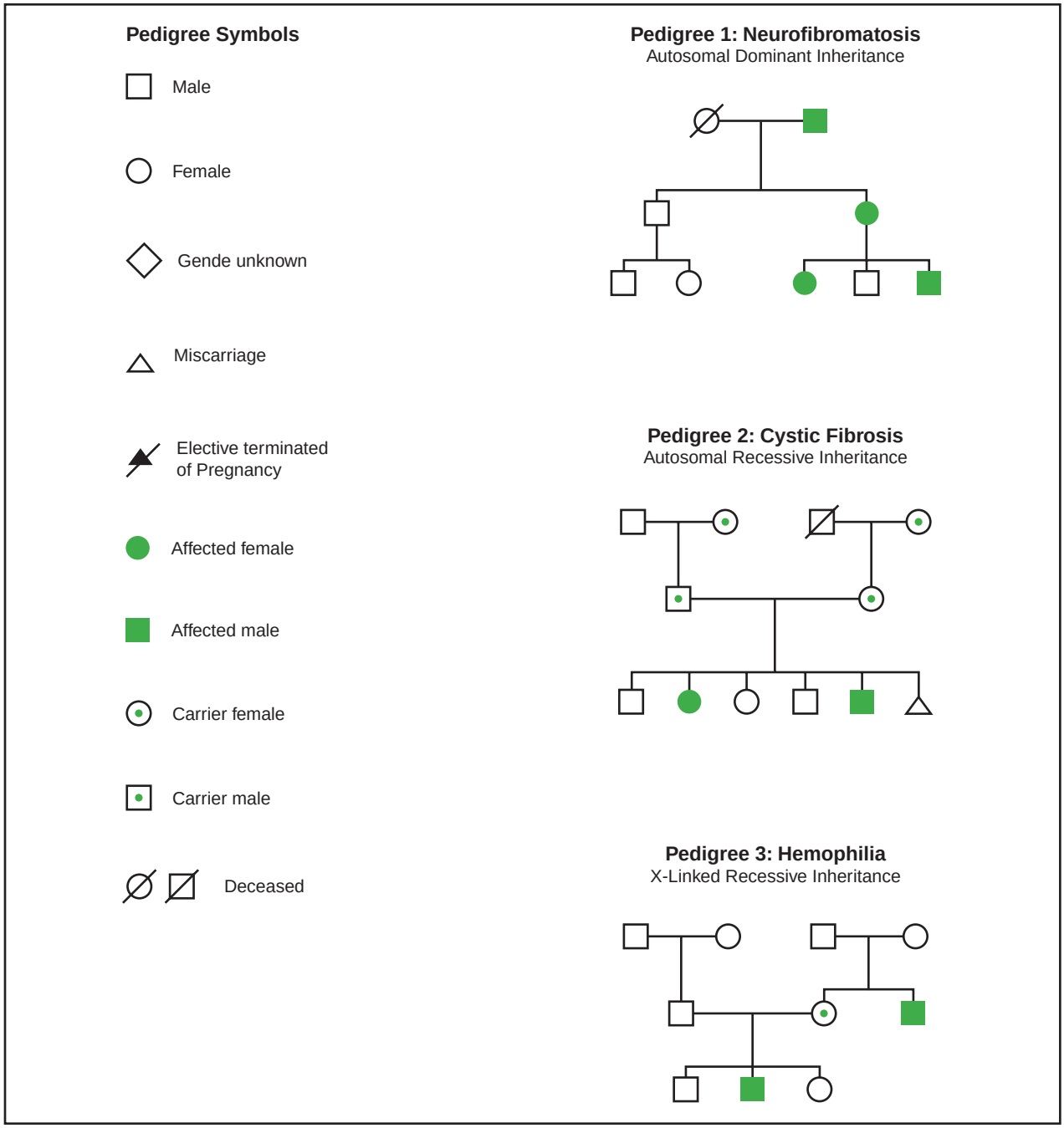
Pedigree patterns

Autosomal dominant inheritance

Pedigree 1 illustrates the occurrence of an autosomal dominant disorder called **neurofibromatosis** (NF). NF is characterized by growths under the skin called neurofibromas, dark spots on the skin called café au lait spots, and an eye finding called Lisch nodules. NF is caused by a single dominant **gene** on chromosome 17. Each person who is affected with NF has a 50% chance to pass the gene on to each child. The symptoms of NF are variable so that some family members are affected more seriously than others. The pedigree shows that in autosomal dominant **inheritance**, multiple generations of a family are affected. This is called vertical transmission of a trait through a family. Males and females are equally likely to be affected. In a particular sibship, about half of the siblings are affected.

Autosomal recessive inheritance

Pedigree 2 illustrates the occurrence of an autosomal recessive disorder called **cystic fibrosis** (CF) in a family. CF is a chronic respiratory disease characterized by digestive problems and a shortened life span. A person with CF has two genes for the condition on chromosome 7. Each parent is an obligate carrier of a gene for the condition. When both parents are carriers, there is a one in four or 25% chance that each child they have together will be affected. In autosomal recessive inheritance, siblings are most often affected rather than people in successive generations. Since siblings are affected, this is called horizontal transmission of a disease in the family. Males and females are equally likely to be affected in this



The illustration above identifies several common symbols used to represent individuals in a pedigree chart. The three pedigree charts to the side provide examples of different types of inheritance patterns and the transmission of abnormal genes through three generations in a family. *(Gale Group)*

type of inheritance and others in the family have an increased chance to be unaffected carriers of the disease.

X-linked recessive inheritance

Pedigree 3 illustrates the occurrence of an X-linked disorder called **hemophilia**. Hemophilia is characterized by excessive bleeding and bruising. Depending on the type of hemophilia, a particular blood-clotting factor is deficient. In X-linked recessive inheritance, males are affected with the condition while females are unaffected carriers. In X-linked recessive inheritance, vertical transmission of the disease is seen, with skipping of generations. There is no male-to-male transmission of a disease in this type of inheritance. This is because males pass

their Y chromosome to each son, instead of the X chromosome with the disease gene. Each daughter of an affected male is an obligate carrier of the disease since they will always inherit his X chromosome. There is a 50% that each son of a carrier woman will be affected. There is a 50% chance that each daughter of a carrier female will be a carrier.

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Sonja Rene Eubanks, MS, CGC

Pelizaeus-Merzbacher disease

Definition

Pelizaeus-Merzbacher disease (PMD) is a neurological condition that affects myelin, the insulation surrounding the nerves in the brain and spinal cord.

Description

PMD was named for two German doctors, F. Pelizaeus and L. Merzbacher, who first described the condition in the late 1800s. The severity of characteristics in PMD can range from mild to severe. PMD primarily affects males, but occasionally females have mild or moderate symptoms. PMD is also called a leukodystrophy, meaning that it affects the myelin, sometimes called the white matter, in the brain and spinal cord. The brain and the spinal cord together are called the central nervous system.

Genetic profile

PMD is caused by a mutation or change in the proteolipid protein **gene** (PLP). The PLP gene has the instructions to make proteolipid protein, one of the proteins that make up myelin in the central nervous system. When there is a mutation in the PLP gene, the myelin is not formed properly or is not made at all, resulting in PMD.

Genes are organized on structures called **chromosomes**. There are hundreds to thousands of genes on each chromosome. There are 46 chromosomes in each cell of the body. These are grouped into 23 pairs. The first 22 pairs are the same in both males and females. The 23rd pair is called the sex chromosomes; having one X chromosome and one Y chromosome causes a person to be male; having two X chromosomes causes a person to be female. A fetus acquires one member of each pair from the mother's egg and one member from the father's sperm.

The PLP gene is located on the X chromosome. Since males have only one X chromosome, they have only one copy of the PLP gene. Thus, a male with a mutation in his PLP gene will have PMD. Females have two X chromosomes and therefore have two copies of the PLP gene. If they have a mutation in one copy of their PLP genes, they may only have mild symptoms of PMD or no symptoms at all. This is because their normal copy of the PLP gene does make normal myelin. Females who have one copy of the PLP gene with a mutation and one normal copy are called carriers.

Inheritance

PMD is passed on through families by X-linked recessive **inheritance**. This means that affected males are related through females in the family. A male does not pass PMD on to his sons. Females pass on one of their X chromosomes to their sons or daughters. If the normal X chromosome is passed on, her son or daughter will be unaffected and cannot pass PMD onto their children. However, if the X chromosome with the PLP mutation is passed on, a daughter will be a carrier while the son would have PMD. Therefore, a female PLP mutation carrier has a 50%, or one in two chance of having a normal child (son or daughter), a 25%, or one in four chance of having a carrier daughter, and a 25%, or one in four chance of having an affected son.

Males with PMD usually do not reproduce and therefore do not pass PMD on.

Mutations

Different types of mutations or changes in the PLP gene cause PMD. Everyone in a family who has the condition or is a carrier has the exact same PLP mutation. The most common type of mutation is a duplication (doubling) of the PLP gene. This means that two copies of the PLP gene are present on one X chromosome. Having this extra copy causes the myelin to be abnormal and leads to PMD. About 50–75% of people with PMD have a PLP

duplication. The duplication usually causes a severe form of PMD. Another 15–20% of people with PMD have point mutations within their PLP gene. A point mutation is like a typo in the gene. This typo changes the message of the gene and also causes the myelin to be abnormal. A few patients with PMD have a deletion of the PLP gene as their cause of PMD. This means that they have no copies of the PLP gene if they are male or one copy if they are female. Another 5–20% of patients have characteristics of PMD, but no mutation has been found in their PLP gene. Scientists are working to determine the cause of disease in these people.

Demographics

PMD has been described in people from all over the world and from many different ethnic backgrounds. The condition is rare and estimated to affect approximately one in 300,000 individuals in the United States.

Signs and symptoms

There is a range in the severity of symptoms of PMD. Rough categories have been set up based on the age of onset and severity of symptoms. However, many patients do not fall neatly into one of these categories and instead fall somewhere in between. Patients with different severities have been seen in the same family.

In the most severe form of PMD, symptoms are first noticed shortly after birth or in infancy. This is called connatal PMD. One of the first signs usually noticed is nystagmus, a side-to-side jerking of the eyes. This does not usually cause problems with vision. Patients can have significant mental retardation and never learn to walk, talk, or care for themselves. They may have noisy breathing called stridor and difficulty sucking. Seizures may be present in these children. They are often small for their age and have trouble gaining weight. Early on, they have floppy muscles called hypotonia, but later develop spasticity, which is stiffness or tightness in the muscles and joints.

Those patients who have classical PMD, which is less severe than the connatal type, usually have nystagmus. Nystagmus develops within the first few months of life. Other symptoms typically develop within the first few years. These children also have hypotonia that turns into spasticity. Sometimes these patients will learn to walk. However, they may need a wheelchair as their spasticity increases. Shaking of the head and neck called titubation may occur. Although these children often have moderate mental retardation, they often learn to talk and often understand more than is evident by their speech.

A less severe type of PMD is called the PLP null syndrome. Those affected do not usually have nystagmus and their spasticity may be mild. Symptoms develop in early childhood. This group of patients may also have a peripheral neuropathy, which is a problem with the nerves that run from the spinal cord through the body. This can cause weakness and problems with sensation (telling if something is hot or cold, for example). These patients usually talk and walk. They may have mild to moderate mental retardation.

There are some people who have PLP mutations who are very mildly affected. They have spasticity and sometimes have other problems such as a spastic bladder. Intelligence is normal or mildly impaired. Although these individuals have mutations in the PLP gene, their condition is given a different name, spastic paraplegia 2 (SPG2).

Diagnosis

When problems are first noticed in an infant or a child, they will usually be referred to a pediatric neurologist who is specially trained in diseases of the nerves and muscles in children. At the initial evaluation, the neurologist will perform a clinical examination to evaluate the child's development and how well the nerves and muscles work. At this time, a thorough family history should be taken to determine if there are others in the family that are affected and if so, how they are related.

One of the initial tests that may be ordered is magnetic resonance imaging (MRI). In this test, pictures of the brain are taken and the amount of white matter in the brain is measured. In people with PMD, the amount of white matter is usually significantly reduced compared to normal. However, a decrease in white matter is seen in other neurological conditions and is not specific to PMD. Therefore, an MRI can be helpful in making the diagnosis of PMD, but if changes are seen on MRI, it does not confirm the diagnosis of PMD. Changes in the white matter may only be seen after one to two years of age when the brain has matured.

If no one else in the family is known to be affected, testing may be performed to rule out conditions other than PMD. Often PMD may not initially be suspected when no one else is affected in the family. It is not uncommon for people to be misdiagnosed initially. Sometimes the diagnosis of PMD is made only after a second affected child is born into a family.

Genetic testing

The only way to be absolutely sure that someone has PMD is by **genetic testing**, usually done by a blood test. First, the genetic material is evaluated to see if a PLP gene duplication is present. If this test is negative, additional testing can be done to look for other mutations in

the gene. In 80% of people who have clear symptoms of PMD, a mutation can be found in the PLP gene. If a mutation in the PLP gene has been identified in a family member, testing on another child suspected of having PMD is possible to look at the mutation known to cause PMD in the family.

Treatment and management

There is no treatment or cure for PMD. Medical management is aimed at making life as full as possible and keeping people free from illness. Different types of therapy might be suggested. An occupational therapist can suggest adaptive devices to make it easier for an affected person to get around his or her home and perform everyday activities such as eating and using the bathroom. For example they may suggest installing bars to use in the bathroom or shower or special utensils for eating. Physical therapy can be helpful for reducing spasticity. Some patients with PMD require a feeding tube to help take in more calories. There are also medications that can assist in treating spasticity and seizures.

Prenatal testing

Testing during pregnancy to determine whether an unborn child is affected is possible if genetic testing in a family has identified a specific PLP mutation. This can be done at 10–12 weeks gestation by a procedure called chorionic villus sampling (CVS), which involves removing a tiny piece of the placenta and examining the cells. It can also be done by **amniocentesis** after 16 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with them. Couples interested in these options should have **genetic counseling** to carefully explore all of the benefits and limitations of these procedures.

Another procedure, called preimplantation diagnosis, allows a couple to have a child that is unaffected with the genetic condition in their family. This procedure is experimental and not available for all conditions. Those interested in learning more about this procedure should check with their doctor or genetic counselor.

Prognosis

The prognosis for patients with PMD varies in part due to the severity of the symptoms. The quality of care that patients receive also makes a difference in their quality of life. Boys with connatal PMD may die in infancy or early childhood, although some have survived into their 30s. Those with classic PMD or with the PLP null syndrome usually reach adulthood, and some have survived into their 70s. The symptoms of PMD usually progress very slowly and some people have a plateau of their symptoms over time. Some people may seem to get worse over time but it is likely to be due to factors such as growth spurts, poor nutrition, or frequent illness and not because of progression of the disease. Most patients with PMD die from pulmonary or breathing difficulties.

KEY TERMS

Central nervous system (CNS)—In humans, the central nervous system is composed of the brain, the cranial nerves and the spinal cord. It is responsible for the coordination and control of all body activities.

Leukodystrophy—A disease that affects the white matter called myelin in the CNS.

Myelin—An insulation that is wrapped around the nerves in the body. In the central nervous system it is also called the white matter.

Nystagmus—Involuntary, rhythmic movement of the eye.

Proteolipid protein gene (PLP)—A gene that makes a protein that is part of the myelin in the central nervous system. Mutations in this gene cause PMD.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

PMD Foundation. Contact: Mike Laprocido, (609) 636-2482.

United Leukodystrophy Foundation. 2304 Highland Dr., Sycamore, IL 60178. (815) 895-3211 or (800) 728-5483. Fax: (815) 895-2432. <http://www. ulf.org>.

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Karen M. Krajewski, MS, CGC

Pendred syndrome

Definition

Pendred syndrome is an inherited condition that causes hearing loss typically beginning at birth and usually leads to the development of an enlarged thyroid, called a goiter. The thyroid is a gland responsible for normal body growth and metabolism. People with Pendred syndrome often have altered development of certain bones in the inner ear and/or balance problems as well. Vaughan Pendred first described the presence of hearing loss and goiter in two sisters in 1896, and thus the condition became known as Pendred syndrome. Genetic research has identified a **gene** on chromosome number seven that is usually altered in people with Pendred syndrome.

Description

Pendred syndrome is sometimes called goiter-sensorineural deafness, due to the common existence of both goiter and a form of hearing loss called sensorineural hearing loss in affected individuals. In order to understand how goiter occurs, it is helpful to first understand how the thyroid gland normally works. The thyroid is located underneath the larynx (voice box), in the front of the neck. The main role of the thyroid is to trap iodine, an essential nutrient found in various foods as well as salt, and to use it to make two important hormones: T3 and T4. These thyroid hormones allow the body to grow normally and to increase the speed of metabolism (breakdown) of nutrients. The thyroid is able to create these hormones because of a series of chemical reactions. A portion of the brain called the hypothalamus is responsible for controlling many body functions. One of its functions is to make a chemical called thyroid releasing hormone (TRH). This hormone travels to another gland, called the anterior pituitary gland, which is located underneath the brain. The TRH stimulates the anterior pituitary gland, which makes a chemical called thyroid stimulating hormone (TSH). This hormone travels to the thyroid, and activates the release of T3 and T4 into the body.

The word goiter is used to describe an enlargement of the thyroid gland. People with goiter may have hypothyroidism (they make too little T3/T4), hyperthyroidism (they make too much T3/T4), or they may have thyroid glands that work normally. Approximately 44–50% of people with Pendred syndrome have hypothyroidism, while the remaining 50–56% have thyroid glands that create a normal amount of thyroid hormones. However, approximately 75% develop goiter at some point in time, although it is rarely present at birth. Thirty to 40% of individuals develop an enlarged thyroid in late childhood or during their early teen-age years. The remaining 60–70% show symptoms during their early adult years. The enlargement of the thyroid gland happens because the mechanisms that control iodine transfer within the cells of the thyroid do not work well. This transfer is necessary to allow the iodine to bind to (and in doing so, help generate) thyroid hormones stored inside the thyroid. Since the iodine is not moved to the correct area of the thyroid, it becomes "pooled," rather than attaching itself to thyroid hormones. This faulty processing of iodine among people with Pendred syndrome can often be confirmed by the use of a perchlorate discharge test. Perchlorate is a chemical that causes the pooled iodine to be pushed out of the thyroid into the bloodstream where it can be measured. Since people with Pendred syndrome usually have more pooled iodine than normal, they will push out or discharge a larger amount of iodine when they are exposed to perchlorate. However, not all affected individuals show abnormal results, so the test is not perfect.

Pendred syndrome causes a specific type of hearing impairment called sensorineural hearing loss (SNHL). The ear can be divided into three main parts: the outer ear, the middle ear, and the inner ear. The parts of the outer ear include the pinna (the visible portion of the ear), the ear canal, and the eardrum. The pinna directs sound waves from the environment through the ear canal, toward the eardrum. The eardrum vibrates, and causes tiny bones (called ossicles), which are located in the middle ear, to move. This movement causes pressure changes in fluids surrounding the parts that make up the inner ear. The main structures of the inner ear are the cochlea and the vestibular system. These structures send information

KEY TERMS

Cochlea—A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

Cochlear implantation—A surgical procedure in which a small electronic device is placed under the skin behind the ear and is attached to a wire that stimulates the inner ear, allowing people who have hearing loss to hear useful sounds.

Enlarged vestibular aqueduct (EVA)—An enlargement of a structure inside the inner ear called the vestibular aqueduct, which is a narrow canal that allows fluid to move within the inner ear. EVA is seen in approximately 10% of people who have sensorineural hearing loss.

Goiter—An enlargement of the thyroid gland, causing tissue swelling that may be seen and/or felt in the front of the neck. May occur in people who have overactive production of thyroid hormones (hyperthyroidism), decreased production of thyroid hormones (hypothyroidism), or among people who have normal production of thyroid hormones.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Pendrin—A protein encoded by the PDS (Pendred syndrome) gene located on chromosome 7q31. Pendrin protein is believed to transport iodide and chloride within the thyroid and the inner ear.

Perchlorate discharge test—A test used to check for Pendred syndrome by measuring the amount of iodine stored inside the thyroid gland. Individuals with Pendred syndrome usually have more iodine stored than normal, and thus their thyroid will release a large amount of iodine into the bloodstream when they are exposed to a chemical called perchlorate.

Sensorineural hearing loss (SNHL)—Sensorineural hearing loss occurs when parts of the inner ear, such as the cochlea and/or auditory nerve, do not work correctly. It is often defined as mild, moderate, severe, or profound, depending upon how much sound can be heard by the affected individual. SNHL can occur by itself, or as part of a genetic condition such as Pendred syndrome.

Thyroid gland—A gland located in the front of the neck that is responsible for normal body growth and metabolism. The thyroid traps a nutrient called iodine and uses it to make thyroid hormones, which allow for the breakdown of nutrients needed for growth, development and body maintenance.

Vestibular system—A complex organ located inside the inner ear that sends messages to the brain about movement and body position. Allows people to maintain their balance when moving by sensing changes in their direction and speed.

regarding hearing and balance to the brain. The cochlea is shaped like a snail shell, and it contains specialized sensory cells (called hair cells) that change the sound waves into electrical messages. These messages are then sent to the brain through a nerve (called the auditory nerve) that allows the brain to "hear" sounds from the environment. The vestibular system is a specialized organ that helps people maintain their balance. The vestibular system contains three structures called semi-circular canals, which send electrical messages to the brain about movement and body position. This allows people to maintain their balance when moving by sensing changes in their direction and speed.

Sensorineural hearing loss occurs when parts of the inner ear (including the cochlea and/or auditory nerve) do not work correctly. The amount (or degree) of hearing loss can be described by measuring the hearing threshold (the sound level that a person can just barely hear) in decibels (dB). The greater a person's dB hearing level, the louder the sound must be to just barely be heard. Hearing loss is often defined as mild, moderate, severe, or profound. For people with mild hearing loss (26–45 dB), understanding conversations in a noisy environment, at a distance, or with a soft-spoken person is difficult. Moderate hearing loss (46–65 dB) causes people to have difficulty understanding conversations, even if the environment is quiet. People with severe hearing loss (66–85 dB) have difficulty hearing conversation unless the speaker is standing nearby or is talking loudly. Profound hearing loss (greater than 85 dB) may prevent people from hearing sounds from their environment or even loud conversation. People with Pendred syndrome generally have severe to profound SNHL that is congenital (i.e. present at birth) in both ears. However, some affected individuals develop SNHL during childhood, after they have learned to speak.

People with SNHL often undergo specialized imaging tests, such as computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, which create detailed images of the tissue and bone structures of the inner ear. Approximately 85% of people affected with Pendred syndrome have physical changes in the inner ear that can be seen with these tests. A common finding is a visible change in the snail-shaped cochlea called a Mondini malformation, in which the cochlea is underdeveloped and has too few coils compared to a normal cochlea. Another visible change sometimes seen in the inner ear is called enlarged vestibular aqueduct. The vestibular aqueduct is a narrow canal that allows fluid to move within the inner ear. Enlarged vestibular aqueduct (EVA) is the most common form of inner ear abnormality that is seen with CT or MRI scans. As the name implies, the vestibular aqueduct (canal) is larger than normal in people with EVA. Although EVA is seen in approximately 10–12% of people who are born with SNHL, some people with EVA can have SNHL that fluctuates (comes and goes) or is progressive (gradually worsening) as well as balance problems. In spite of the fact that Pendred syndrome has typically been diagnosed among people with both SNHL and goiter/thyroid problems, as of 2000, preliminary studies support the finding that some people with EVA and SNHL have a form of Pendred syndrome, even if they do not have goiter or thyroid problems.

Pendred syndrome also causes vestibular dysfunction in approximately 66% of affected individuals, which means they have abnormalities in their vestibular (balance) system. This may cause problems such as dizziness because they cannot sense changes in direction or speed when they are moving.

Genetic profile

Pendred syndrome is inherited in an autosomal recessive manner. “Autosomal” means that males and females are equally likely to be affected. “Recessive” refers to a specific type of **inheritance** in which both copies of a person’s gene pair (i.e. both alleles) need to be changed or altered in order for the condition to develop. In this situation, an affected individual receives an altered copy of the same gene from each parent. If the parents are not affected, they each have one working copy of the gene and one non-working (altered) copy, and are only “carriers” for Pendred syndrome. The chance that two carrier parents will have a child affected with Pendred syndrome is 25% for each pregnancy. They also have a 50% chance to have an unaffected child who is simply a carrier, and a 25% chance to have an unaffected child who is not a carrier, with each pregnancy.

The gene for Pendred syndrome is located on chromosome 7q31 and has been named the PDS gene. The gene tells the body how to make a specific protein called pendrin. The pendrin protein is believed to be responsible for transporting negatively charged elements called iodide and chloride (forms of iodine and chlorine) within the thyroid and likely the inner ear as well. Changes within the PDS gene create an altered form of pendrin protein that does not work properly, and thus causes the symptoms of Pendred syndrome. As of March 2001, genetic researchers identified at least 47 different types of alterations in the PDS gene among different families. However, four of these are more common than the others, and it is estimated that approximately 75% of affected people have these common changes.

Genetic research on the PDS gene has revealed that different types of gene changes can lead to different symptoms. For example, changes that completely inactivate the pendrin protein have been seen among people with Pendred syndrome (i.e. SNHL and goiter), whereas other types of alterations that only decrease the activity of pendrin have been found in people who have an inherited form of deafness called DFNB4. These individuals do have SNHL, but do not develop goiter. The researchers who published this finding in 2000 believed that the small amount of pendrin activity in these individuals likely prevented or delayed the symptoms of goiter. Another study published in 2000 showed that a large portion (greater than 80%) of people with EVA and SNHL were found to have one or more changes in the PDS gene, even though they did not all have thyroid changes such as goiter or abnormal perchlorate discharge test results. Thus, it is believed that changes in the pendrin gene actually cause a number of overlapping conditions. These conditions range from Pendred syndrome (i.e. SNHL and thyroid changes) to SNHL with EVA.

Demographics

Pendred syndrome has been estimated to occur in approximately 7.5 in 100,000 births in Great Britain, and one in 100,000 births in Scandinavia. It has been diagnosed in many different ethnic groups, including Japanese, East Indian, and other Caucasian groups, as well as among people of African descent. Inherited forms of congenital SNHL occur in approximately one of every 2,000 children. Prior to the discovery of the PDS gene, researchers estimated that up to 10% of all children born with SNHL could actually have Pendred syndrome. However, the percentage may be even higher. This is because changes in the PDS gene have been found in people who have SNHL and EVA, even though they do not have thyroid changes that would have helped make a clear diagnosis of Pendred syndrome in the past. Thus,

future genetic studies on large groups of individuals with SNHL will help researchers understand how common Pendred syndrome truly is, as well as the range of symptoms that are caused by changes in the PDS gene.

Signs and symptoms

Although the symptoms of Pendred syndrome can vary among different individuals, the findings may include:

- Sensorineural hearing loss that is usually congenital
- Thyroid changes such as goiter, abnormal perchlorate discharge test results, and/or hypothyroidism
- Inner ear changes, such as enlarged vestibular aqueduct (EVA) or Mondini malformation
- Altered vestibular function that leads to balance problems

Diagnosis

The diagnosis of Pendred syndrome is typically based upon the results from a variety of tests that measure hearing, thyroid appearance/function, inner ear structure, and balance. Sometimes the diagnosis is not made until a person with SNHL reaches adolescence or adulthood and develops thyroid problems such as goiter or hypothyroidism. These problems are usually detected by physical examination and blood tests, and thus help diagnose Pendred syndrome. However, children who are born with SNHL often undergo special imaging tests such as CT or MRI scans. These may show inner ear changes that raise the question of possible changes in the PDS gene, even if the children do not have thyroid problems. In each of these situations, **genetic testing** may provide useful information that can confirm the diagnosis of Pendred syndrome.

Genetic research testing can be done for people with suspected or known Pendred syndrome by studying their **DNA**. The laboratory can check for the four common changes and some unique changes that have been found in the PDS gene. If this testing identifies an affected person's specific genetic changes, other people in the same family who are not affected can have their DNA examined as well. This can determine whether an unaffected person is a carrier for Pendred syndrome or not. In addition, testing could be done during a pregnancy if both of a baby's parents are carriers and have each had specific changes diagnosed in their DNA.

If genetic testing is done for people with known or suspected Pendred syndrome and the laboratory finds only one changed gene or no changes in the PDS gene, the diagnosis of Pendred syndrome cannot be confirmed. However, this does not rule out the possibility of Pendred syndrome. Sometimes this happens simply because the affected person has a very unique change in the PDS gene that the lab cannot clearly identify. Over time, further genetic research could potentially provide useful information about their specific genetic changes as knowledge about the PDS gene grows.

Treatment and management

As of 2001, there is no cure for Pendred syndrome. However, there are several ways to treat some of the symptoms.

Treatment and management of SNHL

Regular visits with an audiologist (a hearing specialist) and an ENT (a physician specializing in the ear, nose, and throat) are important for people with Pendred syndrome. Hearing tests are necessary to check for changes in hearing ability, especially if people have milder forms of hearing loss and have some ability to hear. Among people with milder forms of hearing loss, hearing aids and speech therapy may be useful. However, people with profound SNHL and their families usually benefit from sign language training, which provides a good method of communication. Some people with severe to profound forms of hearing loss may also consider a procedure called cochlear implantation, in which a small electronic device is surgically placed behind the ear (underneath the skin) and is attached to a wire that stimulates the inner ear. This may allow people to hear useful sounds.

Treatment and management of thyroid problems

Regular examinations by an endocrinologist (a physician specializing in the treatment of hormone problems) who is familiar with Pendred syndrome is important. People who develop goiter and/or hypothyroidism are sometimes treated with a medication called thyroxine, which is basically the hormone called T4. Other people with goiter have most of their thyroid surgically removed. However, this form of treatment is not a cure, and the remaining thyroid tissue can grow and redevelop into goiter again. Among some people, the goiter does not require treatment or it simply disappears on its own.

There are a number of support groups available that provide education, support and advice to help people cope with the symptoms of SNHL and thyroid problems that often occur among individuals with Pendred syndrome.

Prognosis

Pendred syndrome does not cause a shortened life span for affected individuals. Those who develop hypothyroidism and do not seek treatment may experience

a variety of health problems including low energy level, weight gain, constipation, and dry skin. However, hypothyroidism and goiter can usually be well managed with medication or surgery. The degree of hearing loss that occurs is typically severe to profound from an early age and usually changes very little over the years. However, among affected people who develop SNHL during childhood (after learning to speak), the degree of hearing loss can worsen over time. Sign language training (and sometimes cochlear implants) allow alternative methods of communication and thus help people reach their full potential. Support groups for people with hearing loss often help individuals with SNHL (whether due to Pendred syndrome or other causes) maintain and/or improve their quality of life as well.

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American Society for Deaf Children. PO Box 3355, Gettysburg, PA 17325. (800) 942-ASDC or (717) 334-7922 v/tty. <http://www.deafchildren.org/asdc2k/home/home.shtml>.

American Thyroid Association. Townhouse Office Park, 55 Old Nyack Turnpike, Ste. 611, Nanuet, NY 10954. <http://www.thyroid.org>.

Boys Town National Research Hospital. 555 N. 30th St., Omaha, NE 68131. (402) 498-6749. <http://www.boystown.org/Btnrh/Index.htm>.

National Association of the Deaf. 814 Thayer, Suite 250, Silver Spring, MD 20910-4500. (301) 587-1788. nadinfo@nad.org. <http://www.nad.org>.

National Institute on Deafness and Other Communication Disorders. 31 Center Dr., MSC 2320, Bethesda, MD 20814. <http://www.nidcd.nih.gov>.

Vestibular Disorders Association. PO Box 4467, Portland, OR 97208-4467. (800) 837-8428. <http://www.vestibular.org>.

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Pamela J. Nutting, MS, CGC

Pepper syndrome *see* **Cohen syndrome**

Perinatal sudanophilic leukodystropy *see* **Pelizaeus-Merzbacher disease**

Peroutka sneeze *see* **Achoo syndrome**

Pervasive developmental disorders

Definition

The pervasive developmental disorders, or PDDs, are a group of childhood disorders that manifest during the first years of the child's life. They are marked by severe weaknesses in several areas of development: social interaction, communication, or the appearance of stereotyped behavior patterns and interests. The PDDs are also known as autistic spectrum disorders. As the phrase *spectrum disorder* suggests, persons with these disorders fall at different points along a fairly wide continuum of disabilities and associated disorders. As defined by DSM-IV, the pervasive developmental disorders include:

- autistic disorder
- **Rett syndrome**
- childhood disintegrative disorder (CDD)
- **Asperger syndrome**
- pervasive developmental disorder not otherwise specified (PDD-NOS)

Description

The PDDs form a diagnostic category intended to identify children with delays in or deviant forms of social, linguistic, cognitive, and motor (muscular movement) development. The category covers children with a wide variety of developmental delays of differing severity in these four broad areas. The precise cause(s) of the

PDDs are still obscure, but are assumed to be abnormalities of the central nervous system.

Autistic disorder

Autistic disorder, or **autism**, was first described in 1943. Autistic children are characterized by severe impairment in their interactions with others and delayed or abnormal patterns of communication; about 50% of autistic children do not speak at all. These abnormalities begin in the first weeks of life; it is not unusual for the parents of an autistic child to say that they "knew something was wrong" quite early in the child's development. Another characteristic symptom has been termed "insistence on sameness;" that is, these children may become extremely upset by trivial changes in their environment or daily routine—such as a new picture on the wall or taking a different route to the grocery store. Autistic children often make repetitive or stereotyped gestures or movements with their hands or bodies. Their behavioral symptoms may also include impulsivity, aggressiveness, temper tantrums, and self-biting or other forms of self-injury.

About 75% of children diagnosed with autism are also diagnosed with moderate mental retardation (IQ between 35 and 50). Their cognitive skills frequently develop unevenly, regardless of their general intelligence level. A minority of autistic children have IQs above 70; their condition is sometimes called high-functioning autism, or HFA. In addition to mental retardation, autism is frequently associated with other neurological or medical conditions, including encephalitis, phenylketonuria, **tuberous sclerosis**, **fragile X syndrome**, and underdeveloped reflexes. About 25% of autistic children develop seizure disorders, most often in adolescence.

Rett syndrome

Unlike autism, Rett syndrome has a very distinctive onset and course. The child develops normally during the first five months of life; after the fifth month, head growth slows down and the child loses whatever purposeful hand movements she had developed during the first five months. After 30 months, the child frequently develops repetitive hand-washing or hand-wringing gestures; over 50% of children with the disorder will develop seizure disorders. Rett syndrome is also associated with severe or profound mental retardation. As of 2001, this disorder has been diagnosed only in females.

Childhood disintegrative disorder (Heller's syndrome)

Childhood disintegrative disorder, or CDD, was first described by an educator named Theodore Heller in 1908. He referred to it as *dementia infantilis*. Children with CDD have apparently normal development during the first two years of life. Between two and ten years of age, the child loses two or more previously acquired skills, including language skills, social skills, toileting, self-help skills, or motor skills. The child may also lose interest in his or her surroundings, and often comes to "look autistic." The data available as of 2001 indicate that CDD has several different patterns of onset and development; it may develop rapidly (within weeks) or more slowly (over a period of months).

CDD is frequently associated with severe mental retardation. In addition, children with CDD have a higher risk of seizures. CDD is occasionally associated with general medical conditions (metachromatic leukodystrophy or Schilder's disease) that could account for the developmental losses, but in most cases there is no known medical cause of the child's symptoms.

Asperger syndrome

Asperger syndrome (AS) was first identified in 1944 by a Viennese psychiatrist. It is sometimes called autistic psychopathy. AS is distinguished from autism by later onset of symptoms; these children usually develop normally for the first few years of life and retain relatively strong verbal and self-help skills. They are often physically clumsy or awkward, however, and this symptom may be noticed before the child starts school. AS is diagnosed most frequently when the child is between five and nine years of age. One of the distinctive features of Asperger syndrome is an abnormal degree of fascination or preoccupation with a limited or restricted subject of interest, such as railroad timetables, the weather, astronomical data, French verb forms, etc. In addition, the child's knowledge of the topic reflects rote memorization of facts rather than deep understanding.

Unlike autism, AS does not appear to be associated with a higher risk of seizure disorders or such general conditions as fragile X syndrome.

Pervasive developmental disorder not otherwise specified

PDD-NOS is regarded as a "sub-threshold" category, which means that it covers cases in which the child has some impairment of social interaction and communication, or has some stereotyped patterns of behavior, but does not meet the full criteria for another PDD. PDD-NOS is sometimes referred to as atypical personality development, atypical autism, or atypical PDD. No diagnostic criteria specific to this category are provided in DSM-IV. Little research has been done on children diagnosed with PDD-NOS because the condition has no clear definition. The available data indicate that children

KEY TERMS

Atypical personality development—Another term for pervasive development disorder (PDD-NOS). Other synonyms for this diagnostic category are atypical autism and atypical PDD.

Autistic psychopathy—Hans Asperger's original name for Asperger syndrome. It is still used occasionally as a synonym for the disorder.

Autistic spectrum disorders—Another term for the pervasive developmental disorders.

Heller's syndrome—Another name for Childhood Disintegrative Disorder (CDD). It is also sometimes called dementia infantilis.

Kanner's syndrome—Another name for autism.

placed in this category are diagnosed at later ages than children with autism, and are less likely to have mental impairment.

Genetic profile

Of the PDDs, autism has the best-documented genetic component, although more research is required. It is known that the degree of similarity in a pair of twins with respect to autism is significantly higher in identical than in fraternal twins. The likelihood of the biological parents of an autistic child having another child with the disorder is thought to be about 1:20. It is possible that the actual rate is higher, since many parents of one autistic child decide against having more children.

The genetic profile of Asperger syndrome is less well known, although the disorder appears to run in families—most commonly families with histories of **depression** or **bipolar disorder**. Rett syndrome is known only from case studies, so data about its genetic profile is not available as of 2001. The same lack of information is true also of CDD—partly because the disorder was first reported in 1966 and has only been officially recognized since 1994, and partly because the condition has been frequently misdiagnosed.

Demographics

Autism is thought to affect between two and five children out of every 10,000. Childhood disintegrative disorder is much less frequent, perhaps only a tenth as common as autism. Rett syndrome is also very rare, and is known only from case series reported in the medical literature. The incidence of Asperger syndrome is not definitely known as of 2001, but is thought to lie somewhere between 0.024% and 0.36% of the general population.

Some of the PDDs are considerably more common in boys than in girls. The male to female sex ratio in autism is variously given as 4:1 or 5:1. Less is known about the incidence of Asperger syndrome, but one study reported a male/female ratio of 4:1. Initial studies of CDD suggested an equal sex ratio, but more recent data indicate that the disorder is more common among males. Rett syndrome, on the other hand, has been reported only in females.

Signs and symptoms

The signs and symptoms of each PDD are included in its description.

Diagnosis

The differential diagnosis of autistic spectrum disorders is complicated by several factors. One is the wide variation in normal rates of children's development. In addition, because some of the symptoms of autism are present in mental retardation, it can be difficult to determine which condition is present in a specific child, or whether both conditions are present. A definitive diagnosis of autism is rarely given to children below the age of three years. Delays or abnormal patterns in cognitive and social development can be more accurately assessed in children age three or four; children with AS or PDD-NOS may not be diagnosed until age five or later. A third factor is the tangled history of differential diagnosis of childhood disorders. Autism was first described by a physician named Leo Kanner in 1943. For several decades after Kanner's initial observations, researchers assumed that there was an association or continuity between autism in children and **schizophrenia** in adults. In fact, the term *autism* was first used to describe the self-focused thinking that characterizes schizophrenia; it was only later that the word was applied to the severe impairment of social behaviors that is a major symptom of autistic disorder. It took years of further research to establish clear diagnostic distinctions between autism and schizophrenia. Furthermore, the early assumption of a connection between autism and schizophrenia led to the hypothesis that autism was caused by painful experiences in early childhood. It is now known that autism and the other PDDs are essentially neurological disturbances.

Medical or laboratory testing

As of 2001, there are no brain imaging studies or laboratory tests that can be performed to diagnose a per-

vasive developmental disorder. The examiner may, however, recommend a hearing test to rule out deafness as a possible cause of a child's failure to respond to the environment, or a brain scan to rule out other physical conditions.

Diagnostic interviews

A PDD may be diagnosed by a pediatrician, pediatric neurologist, psychologist, or specialist in child psychiatry. The diagnosis is usually based on a combination of the child's medical and developmental history and clinical interviews or observations of the child. Children who cannot talk can be evaluated for their patterns of nonverbal communication with familiar as well as unfamiliar people. The parents may be asked to describe the child's use of eye contact, gestures, facial expressions, and body language. A clinical psychologist can administer special tests designed to evaluate the child's problem-solving abilities without the use of language.

Diagnostic questionnaires and other tools

The examiner may use a diagnostic checklist or screener such as the Childhood Autism Rating Scale, or CARS, which was developed in 1993. In addition, the Autism Research Institute (ARI) distributes a Form E-2 questionnaire that can be completed by the parents of a child with a PDD and returned to ARI. Form E-2 is not a diagnostic instrument as such but a checklist that assists ARI in the compilation of a database of symptoms and behaviors associated with autistic spectrum disorders. Parents who complete the form will receive a brief report about their child. Researchers expect that the database will help to improve the accuracy of differential diagnosis as well as contribute to more effective treatments for children with PDDs.

Treatment and management

The treatment and management of children with PDDs will vary considerably according to the severity of the child's impairment and the specific areas of impairment.

Medications

As of 2001, there are no medications that can cure any of the PDDs, and no single medication that is recommended for the symptoms of all children with PDDs. In addition, there are few comparative medication studies of children with autistic spectrum disorders. The five sites (UCLA, University of Indiana, Ohio State, Yale, and the Kennedy-Krieger Institute) involved in the Research Units in Pediatric Psychopharmacology (RUPP) Program are currently conducting a study of respiridone in PDD children with behavioral problems. The RUPP sites are also testing medications approved for use in adults with self-injuring behaviors, anxiety, aggressive behavior, and obsessive-compulsive disorder on children with PDDs. This research is expected to improve the available treatments for children with these disorders.

Psychotherapy

The only PDD patients who benefit from individual psychotherapy are persons with AS or with HFA who are intelligent enough to have some insight into their condition. Typically they become depressed in adolescence or adult life when they recognize the nature and extent of their social disabiliities.

Educational considerations

Most children with AS and some children with high-functioning autism are educable. Many people with AS, in fact, successfully complete graduate or professional school. Only a small percentage of autistic children, however, complete enough schooling to be able to live independently as adults. Children with CDD must be placed in schools for the severely disabled.

Employment

Most children with AS can finish school and enter the job market. They do best, however, in occupations that have regular routines or allow them to work in isolation. Only a few high-functioning autistic children are potentially employable.

Prognosis

The PDDs as a group are lifelong disorders, but the prognoses vary according to the child's degree of impairment. As a general rule, language skills and the child's overall IQ are the most important factors in the prognosis. Children with AS have the most favorable educational prognosis but usually retain some degree of social impairment even as adults. Of autistic children, only about one-third achieve partial or complete independence in adult life. The prognoses for Rett syndrome and CDD are worse than that for autism, as the skill levels of these children often continue to deteriorate. Some, however, make very modest developmental gains in adolescence. Lastly, current information about the prognoses of children with PDDs is derived from treatments given to patients in the 1970s or 1980s. As knowledge of effective treatments for PDDs continues to accumulate, children with these disorders receive treatment earlier than they did two decades ago. It is likely that future prognoses for the PDDs will reflect these improvements.

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Autism Research Institute. 4182 Adams Ave., San Diego, 92116. Fax: (619) 563-6840.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Yale-LDA Social Learning Disabilities Project. Yale Child Study Center, 230 South Frontage Road, New Haven, CT 06520-7900. (203) 785-3488. <http://info.med.Yale.edu/chldstdy/autism>.

WEBSITES

Center for the Study of Autism Home Page, maintained by Stephen Edelson, PhD. <http://www.autism.org>.

Yale Child Study Center. <http://info.med.Yale.edu/chldstdy/autism>.

Rebecca J. Frey, PhD

Peutz-Jeghers syndrome

Definition

Peutz-Jeghers syndrome (PJS) is named after two doctors who first studied and described it in 1921. It is an association of three very specific conditions in any one person. The first condition is the appearance of freckles on parts of the body where freckles are not normally found. The second condition is the presence of multiple gastrointestinal polyps. The third condition is a risk, greater than the risk seen in the general population, of developing certain kinds of cancers.

Description

The freckles associated with PJS are dark brown, dark blue, or greenish black. In almost all people with PJS, these freckles are present at birth on the lining of the cheeks inside the mouth. By the time most children reach one or two years old, freckles develop around the lips, nostrils, eyes, anus, and genitals. This is in contrast to ordinary freckles, which are absent at birth and rarely develop in these locations. The freckles seen in PJS are sometimes called macules (discolored spot or patch on the skin of various colors, sizes, and shapes), or areas of hyperpigmentation (increased pigmentation of the skin).

Some people with PJS also have these freckles on the palms of their hands or feet or on their fingertips. Freckles may merge together. The freckles on the skin often fade or disappear by adolescence, but the freckles inside the mouth generally remain throughout the person's life.

Gastrointestinal polyps can develop in children as young as one or two years old. The age at which polyps appear and the number of polyps vary widely from patient to patient. The polyps can occur in infants and cause spasms and pain in the abdomen. On average, polyps appear by the time a child with PJS is 10 years old. There may be anywhere from dozens to hundreds of polyps throughout the gastrointestinal tract. For this reason, PJS is sometimes called polyposis, which means "too many polyps." Most PJS polyps occur in the small intestine, but they can also develop in the esophagus, stomach, and colon. In some people with PJS, polyps have been found in the mouth or nose.

The polyps seen in PJS have a unique structure. They consist of overgrowths of normal tissue that smooth muscle bands of the stomach and instestines run through. This kind of overgrowth is called a hamartoma. Consequently, PJS is sometimes called hamartomatous intestinal polyposis. A hamartoma is a non-cancerous tumor, and hamartomatous polyps are not cancerous. However, they can take up too much space, causing obstruction, pain, and even bleeding. They can also become cancerous, or malignant, if a genetic change results in uncontrolled cell growth.

It is this potential for malignant change that increases **cancer** risk in people with PJS. As might be expected, the gastrointestinal tract is the most common site for cancer in people with PJS. The small intestine, stomach, gallbladder, pancreas, colon, and rectum are all susceptible. However, cancer can also occur outside the gastrointestinal tract. When this happens, the sites most likely to be involved are the breasts, ovaries, uterus, cervix, or testicles.

PJS does not affect intelligence or behavior.

Genetic profile

Researchers have identified the **gene** responsible for about seven out of ten PJS cases. The gene is named STK11, and it is located at the 19p13 site on chromosome 19. In some older studies, the same gene is referred to as LKB1. As of 2001, researchers have connected more than 50 different STK11 mutations to cases of PJS.

However, some cases do not appear to be connected to STK11. As a result, PJS qualifies as a genetically heterogeneous condition; this means that it has more than one known genetic cause. Research continues in order to locate the genes involved in the three out of ten cases not related to STK11.

When linked to STK11, PJS is an autosomal dominant disorder. This means that the condition occurs even when an individual inherits only one abnormal copy of STK11 from either parent. In some people with PJS, the condition is limited to freckles on the lining of the cheeks inside the mouth. Many of these people also have gastrointestinal polyps. One abnormal copy of STK11 also increases a person's risk of developing the kinds of cancer associated with PJS.

However, since only one abnormal copy of STK11 is needed to cause PJS, most people with the condition still have one normal copy of the gene. One normal copy is usually enough to protect against the kinds of cancer associated with PJS. This is because STK11 is a tumor suppressor gene. A properly working tumor suppressor gene makes a product that controls cell growth. Since cancer is the result of uncontrolled cell growth, tumor suppressors prevent cancer. Even one working copy of STK11 protects against cancer.

The reason people with PJS have an increased risk of developing cancer is that one STK11 gene is already abnormal at birth. If damage to the normal STK11 gene occurs later, the ability to control cell growth is lost, leading to the kinds of cancers associated with PJS.

Damage to normal genes can occur in anyone. However, it generally takes less time to damage one gene than two genes. Therefore, people with PJS are likely to develop cancer at earlier ages than are people born with two normal STK11 genes.

About half of all PJS cases occur because a child inherits a changed gene from a parent with PJS. The other half are due to a mutation in the cell from which the child develops. A person born with one abnormal gene can pass that gene on to the next generation. One out of two of this person's children will inherit the gene. In addition, if PJS is inherited, each parent or sibling of the affected person has a one out of two chance of carrying the gene.

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Colon—The large intestine.

Colonoscopy—Procedure for viewing the large intestine (colon) by inserting an illuminated tube into the rectum and guiding it up the large intestine.

Endoscopy—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

Enteroscopy—A procedure used to examine the small intestine.

Esophagus—The part of the digestive tract which connects the mouth and stomach; the foodpipe.

Gastrointestinal—Concerning the stomach and intestine.

Hamartoma.—An overgrowth of normal tissue.

Hyperpigmentation.—An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

Laparoscopy—A diagnostic procedure in which a small incision is made in the abdomen and a slender, hollow, lighted instrument is passed through it. The doctor can view the ovaries more closely through the laparoscope, and if necessary, obtain tissue samples for biopsy.

Macule—A flat, discolored spot or patch on the skin.

Mammogram—A procedure in which both breasts are compressed/flattened and exposed to low doses of x rays, in an attempt to visualize the inner breast tissue.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Polypectomy—Surgical removal of polyps.

Tumor suppressor gene—Genes involved in controlling normal cell growth and preventing cancer.

Demographics

PJS occurs in about one out of 25,000 people. It affects males and females of all races and ethnic groups. The particular genetic mutation may differ among groups and even among families within a group.

Signs and symptoms

The first sign of PJS, freckling inside the mouth or in unusual places, generally appears in infants. Polyps usually begin causing symptoms by age 10. Polyps make themselves known in a variety of ways. They can cause abdominal pain or intestinal bleeding. Sometimes the blood loss leads to anemia (a condition where there is a reduction in circulating red blood cells, the amount of hemoglobin, or the volume of packed red cells). Polyps sometimes protrude outside the rectum or obstruct the gastrointestinal tract. Untreated obstructions can be fatal.

Tumors may appear in childhood. Children as young as six may develop a particular kind of ovarian or testicular tumor that causes early puberty. Affected boys sometimes begin to develop breasts. These tumors can be non-cancerous, but they have the potential to become malignant.

A few patients develop malignant tumors in the first decade of life. Other patients have stomach, breast, or cervical cancer before age 30. The specific form of cervical cancer is extremely rare in the general population.

Diagnosis

Because the peculiar freckling seen in PJS is present so early, doctors familiar with the condition may suspect PJS even before other symptoms occur. This is ideal, since early diagnosis greatly improves the prognosis.

Many children or young adults come to medical attention due to the pain, bleeding, or anemia caused by polyps. Doctors can confirm the presence of multiple polyps using a variety of methods. Noninvasive methods include ultrasound and x ray techniques. Invasive methods use a tube and an optical system to conduct an internal inspection of the gastrointestinal tract. These methods include endoscopy, enteroscopy, and colonoscopy, all of which involve entry to the gastrointestinal tract through an existing body orifice. Laparoscopy is another invasive method; it involves entering the gastrointestinal tract through an incision in the abdomen. All invasive methods allow for removal of polyps found during the exam. Once the polyps are removed and examined, their unique structure and large number lead to diagnosis of PJS. The average age at PJS diagnosis is 17.

Freckles and polyps occur in more than 95% of people with PJS. Sometimes, though, the freckles fade before symptoms of polyps appear. It is important to take a medical history in order to determine if freckles were present on the skin earlier in life. The doctor should also examine the lining of the cheeks inside the mouth, where freckles are likely to remain throughout life.

The number and intensity of the freckles do not predict the severity of gastrointestinal symptoms or the risk of developing cancer. Any patient diagnosed with PJS needs regular cancer screening.

The presence of the rare cervical cancer, ovarian tumor, or testicular tumor associated with PJS leads to diagnosis in some patients.

A family history of PJS is suspicious but not required for diagnosis, since PJS can occur as a new mutation. Once PJS has occurred in a family, parents, siblings, and children of the affected person should seek medical attention.

Genetic testing is available to confirm clinical diagnosis or to determine if a person carries an abnormal STK11 gene. Using a swab, cells are removed from the lining of the cheeks inside the mouth. **DNA** is extracted and analyzed. The test confirms PJS if analysis reveals an STK11 mutation. However, the test cannot rule out PJS if an STK11 mutation is not found, since some cases are due to other genetic causes.

Prenatal diagnosis of PJS is possible only if the family's specific STK11 mutation has previously been identified. Prenatal testing is done by **amniocentesis** or chorionic villus sampling. Amniocentesis involves removal of a small amount of amniotic fluid from the uterus. Chorionic villus sampling involves removal of a small sample of placental tissue. In either case, DNA is extracted from sample cells and analyzed.

Even without genetic testing, diagnosis of PJS is fairly straightforward. Although several other conditions cause multiple intestinal polyps or hyperpigmentation, the distinctive structure of PJS polyps and the unusual location of PJS freckles eliminate other conditions from consideration.

Treatment and management

For people with a family history of PJS, treatment and management of the condition may begin even before diagnosis. If PJS freckles do not appear at birth and if there are no symptoms of polyps, affected families may desire genetic testing for their children.

For most genetic conditions, testing is delayed until children are old enough to understand the disease, its consequences, and the advantages and disadvantages of genetic screening. However, since PJS can affect children under the age of 10, any delay could be risky. Therefore, it is appropriate for families with PJS to consider genetic testing for their children. Children who do carry an STK11 mutation can begin a preventive care program immediately, and children who do not carry an STK11 mutation can avoid unnecessary intervention.

The decision to seek genetic testing requires careful consideration. A positive test for PJS cannot predict the

precise age of onset, symptoms, severity, or progress of the condition. A genetic counselor can assist interested family members as they confront the medical, social, personal, and economic issues involved in genetic testing.

Parents, siblings, and children of people with STK11 mutations may not wish to undergo genetic testing. In this case, they should have a thorough clinical exam to confirm or rule out PJS. The exam includes a careful inspection for freckles. In addition, people age 10 or older require gastrointestinal screening, abdominal ultrasound, and a blood test for anemia. Males over age 10 should have a testicular exam. Females should have a pelvic exam and ultrasound, pap smear, and breast exam annually, by age 20. Women age 35 or older should have a mammogram.

For people with no family history of PJS, treatment and management usually begin when PJS is diagnosed.

In past generations, polyp complications such as intestinal obstruction or hemorrhage were a frequent cause of death in PJS patients. However, treatment of polyps is now widely available. The doctor performs a polypectomy to remove the polyps. Polypectomy may be done at the same time as endoscopy, enteroscopy, colonoscopy, or laparoscopy. Anesthesia is used to make the patient more comfortable.

To manage polyps and screen for early signs of cancer, all people who have PJS and are age 10 or older need preventive screening on a regular basis. Gastrointestinal screening is the first test, and polypectomy is performed at the same time. Also at age 10, the person begins an annual screening program that includes a blood test for anemia and a testicular exam for boys.

After age 10, gastrointestinal screening with polypectomy is performed every two years.

By age 20, annual screening is expanded to include an abdominal ultrasound for both males and females, as well as a pelvic exam and ultrasound, pap smear, and breast exam for females.

By age 35, a woman with PJS should have her first mammogram; mammograms should be repeated every two years until the woman is 50. At that time, a mammogram should be added to the annual screening program.

Polyps found during preventive screening are immediately treated by polypectomy. Preventive screening may also reveal suspicious growths in the gastrointestinal tract or outside of it. These growths require urgent medical attention, since they may be precancerous or cancerous. Diagnosis may require additional tests or biopsy. Treatment is determined on an individual basis, depending on the patient's medical condition and the nature of the growth.

Some people with PJS do not care for the appearance of their freckles. Removal of freckles using laser therapy is an available treatment option.

Many people with PJS find the preventive screening program psychologically exhausting, and young children can find it frightening. These individuals often need the ongoing support and understanding of friends, family, and community. Several organizations composed of people with PJS, their family members, and medical professionals offer additional support and information. There is also an on-line support group dedicated to PJS.

People with PJS may find it helpful to consult a genetic counselor. Genetic counselors can provide up-to-date information about PJS research, therapy, and management.

Prognosis

Early detection of PJS is the key to its prognosis. Polyps cause less pain and fewer complications when found and removed early. In addition, the patient can begin a preventive screening program at an early age. This increases the likelihood of finding suspicious growths before they become malignant.

Unless they undergo regular screening, people with PJS have a one in two chance of dying from cancer before the age of 60. Moreover, the average age of cancer death in unscreened people with PJS is 39.

Researchers are actively investigating cancer screening, prevention, and treatment methods. In the meantime, regular preventive screening may reduce the illness and premature death associated with PJS.

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ORGANIZATIONS

Genetic Alliance. 4301 Connecticut Ave. NW, #404, Washington, DC 20008-2304. (800) 336-GENE (Help-

line) or (202) 966-5557. Fax: (888) 394-3937 info @geneticalliance. <http://www.geneticalliance.org>.

Hereditary Colon Cancer Association (HCCA). 3601 N 4th Ave., Suite 201, Sioux Falls, SD 57104. (800) 264-6783. <http://hereditarycc.org>.

IMPACC (Intestinal Multiple Polyposis and Colorectal Cancer). PO Box 11, Conyngham, PA 18219. (570) 788-1818.

International Peutz-Jeghers Support Group. Johns Hopkins Hospital, Blalock 1008, 600 North Wolfe St., Baltimore, MD 21287-4922.

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Avis L. Gibons

Pfeiffer syndrome

Definition

Pfeiffer syndrome is one of a group of disorders defined by premature closure of the sutures of the skull, resulting in an abnormal skull shape. People affected with these conditions, known as craniosynostosis syndromes, may also have differences in facial structure and hand and foot abnormalities. The defining features of Pfeiffer syndrome are abnormalities of the hands, feet, and shape of the skull.

Description

Pfeiffer syndrome is a complex disorder. Three subtypes of Pfeiffer have been defined based on symptoms. The syndrome is caused by a mutation (alteration) in either of two different genes. As the genes that cause **craniosynostosis** syndromes were discovered throughout the 1990s, scientists realized that these syndromes have overlapping underlying causes. Crouzon, Apert, Jackson-Weiss, and other syndromes are related to Pfeiffer syndrome by genetic causation as well as associated symptoms. Noack syndrome, once thought to be a separate condition, is now known to be the same as Pfeiffer syndrome. Acrocephalosyndactyly, Type V (ACS5) and Noack syndrome both refer to Pfeiffer syndrome.

Genetic profile

Pfeiffer syndrome is an autosomal dominant condition. Every person has two copies of every **gene**, one maternally inherited and one paternally inherited. Autosomal dominant conditions occur if a person has a change in one member of a gene pair. The chance for an affected individual to have an affected child is 50% with each pregnancy.

A person who has an autosomal dominant condition may have it because he or she inherited the altered gene from an affected parent or because of a new mutation. A new mutation occurs when the gene is altered for the first time in that individual. A person with an autosomal dominant condition due to a new mutation is the first person in his or her family to be affected.

Nearly all of the individuals with Pfeiffer syndrome types 2 and 3 described in the medical literature have new mutations. When a person has a new mutation, his or her parents are usually not at risk to have another child with the condition. The milder form, Pfeiffer syndrome type 1, is more likely to be inherited. When the mutation is inherited, the child's symptoms are often similar to those of the affected parent. Pfeiffer syndrome is fully penetrant. This means that all of the individuals who have the mutated gene associated with the condition are expected to have symptoms. In other words, the mutant gene is always expressed.

The two genes that cause Pfeiffer syndrome are called FGFR1 and FGFR2. FGFR1 is on chromosome 8. FGFR2 is on chromosome 11. These genes are members of a group of genes called the "fibroblast growth factor receptors."

Fibroblasts play an important role in the development of connective tissue (e.g. skin and bone). Fibroblast growth factors (FGFs) stimulate certain cells to divide, differentiate (specialize to perform a specific function different than the function of the original cell), and migrate. FGFs are important in limb development, wound healing and repair, and other biological processes. FGFs communicate with targeted cells through the action of the fibroblast growth factor receptors. Fibroblast growth factor receptors (FGFRs) on the targeted cells bind the FGFs and relay their message within the cell.

In 1999, 11 conditions were known to be caused by mutations in three of the four FGFR genes. However, only one condition is present in each affected family. Mutations in FGFR2 may cause Pfeiffer syndrome as well as Apert, Jackson-Weiss, and Crouzon syndromes. Nonetheless, a parent with Pfeiffer syndrome is at risk to

have a child with Pfeiffer but is not at risk to have a child with Crouzon, Apert, or Jackson-Weiss syndromes. Because family members in multiple generations all have the same condition, the condition is said to "breed true" within families. A few exceptions—families with more than one FGFR-associated condition—are reported in the medical literature.

A given genetic condition may be associated with mutations in one particular gene, and mutations in a given gene may cause only one genetic condition. Alternatively, mutations in a gene may be associated with more than one genetic condition, and a particular genetic condition may be caused by any mutation in a number of multiple genes. FGFR2 causing both Pfeiffer and Apert syndromes is an example of the former; FGFR1 and FGFR2 causing Pfeiffer syndrome is an example of the latter. Various mutations of a particular gene are called alleles. Sometimes a gene causes different genetic conditions because each allele leads to a specific set of symptoms.

The exact same mutation in the FGFR2 gene may cause Pfeiffer syndrome in one family and cause a different craniosynostosis syndrome in another family. However, each family continues to have the same symptoms (the conditions breed true in each family). Differing effects of genes are sometimes explained by differing environmental influences and by differing interactions with other genes. However, the diverse effects of the FGFR2 gene probably have a more specific explanation/mechanism. The underlying reasons for these phenomena may be explained when fibroblast growth factors and their receptors are better understood. At that time, criteria defining various craniosynostosis syndromes (e.g. Pfeiffer, Crouzon, and Jackson-Weiss) may be re-examined and revised.

Demographics

The incidence of Pfeiffer syndrome is approximately one in 100,000. The incidence of craniosynostosis is one in 2,000 to one in 2,500, which includes syndromic and nonsyndromic cases. In non-syndromic cases, the craniosynostosis is an isolated finding; no other abnormalities are present. Non-syndromic craniosynostosis is much more common than syndromic craniosynostosis. Usually isolated craniosynostosis is sporadic (not familial).

Signs and symptoms

Individuals with Pfeiffer syndrome have a high forehead, a "tower shaped" skull, and broad, deviated thumbs and great toes. The symptoms of type 1 are milder than those of types 2 and 3. Undergrowth of the midface leads to down-slanting, low-placed, widely spaced eyes; a small upper jaw bone; and a low nasal bridge. The larynx (voice organ below the base of the tongue) and the pharynx (tube that connects the larynx to the lungs) may be abnormal. Additional symptoms include a projecting chin, divergent visual axes, abnormalities of the passage between the nose and the pharynx, and hearing loss. Fingers and toes may be short and/or partially grown together. The palate may be especially high, and teeth may be crowded. In type 2, the elbow joint is frozen in place.

KEY TERMS

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Suture—"Seam" that joins two surfaces together.

The skull is composed of many bones that fuse when the brain has finished growing. If the bones of the skull fuse prematurely (craniosynostosis), the skull continues to grow in an abnormal pattern. The places where the bones of the skull fuse are called sutures.

The suture that fuses prematurely in Pfeiffer syndrome is the coronal suture. This suture separates the frontal bone of the skull from the two middle bones (called the parietal bones). When the coronal suture closes prematurely, upward growth of the skull is increased and growth toward the front and back is decreased. Sometimes the sagittal suture will also be fused prematurely in individuals with Pfeiffer syndrome. This suture separates the right and left sides of the middle of the skull. If both the coronal and sagittal sutures fuse prematurely, the skull develops a somewhat cloverleaf shape. Individuals with Pfeiffer type 2 have cloverleaf skulls more often than individuals with types 1 and 3.

The coronal suture is also fused prematurely in Crouzon, Jackson-Weiss, Apert, and Beare-Stevenson syndromes. The thumbs and big toes are normal in Beare-Stevenson and Crouzon syndromes. Additional associated abnormalities distinguish Apert and Jackson-Weiss syndromes.

Serious complications of Pfeiffer syndrome include respiratory problems and **hydrocephalus**. Hydrocephalus is excessive fluid in the brain, which leads to mental impairment if untreated. Breathing problems may be caused by trachea abnormalities or be related to under-

growth of the midface. Some individuals may require an incision in the trachea (tracheostomy). Serious complications are more common in Pfeiffer types 2 and 3. Individuals with types 2 and 3 are severely affected, and often do not survive past infancy. Death may result from severe brain abnormalities, breathing problems, prematurity, and surgical complications. Even without accompanying hydrocephalus, developmental delays and mental retardation are common (in types 2 and 3). Lower displacement of the eyes may be so severe that the infant is unable to close his or her eyelids. Individuals with types 2 and 3 may also have seizures. Intellect is usually normal in Pfeiffer type 1.

Diagnosis

The diagnosis of Pfeiffer syndrome is based primarily on clinical findings (symptoms). Although **genetic testing** is available, the diagnosis is usually made based on physical examination and radiological testing.

Often the doctor can determine which cranial suture closed prematurely by physical examination. For confirmation, an x ray or computerized tomography (CT) scan of the head may be performed. Determining which suture is involved is crucial in making the correct craniosynostosis diagnosis.

Craniosynostosis may be caused by an underlying genetic abnormality, or it may be due to other, nongenetic factors. In Pfeiffer syndrome, the tissue itself is abnormal and causes the suture to fuse prematurely. The doctor will consider nongenetic causes of craniosynostosis. These secondary causes include external forces such as abnormal head positioning (in the uterus or in infancy) and a small brain.

Genetic testing may be useful for prenatal diagnosis, confirmation of the diagnosis, and to provide information to other family members. Mutations are not detected in all individuals with Pfeiffer syndrome. Approximately one-third of affected individuals with Pfeiffer syndrome do not have an identifiable mutation in the FGFR1 or FGFR2 gene. People with Pfeiffer syndrome due to a mutation in the FGFR1 gene may have less severe abnormalities than people who have Pfeiffer due to mutations in the FGFR2 gene.

Prenatal diagnosis is available by chorionic villus sampling (CVS) or **amniocentesis** if a mutation has been identified in the affected parent. Amniocentesis is performed after the fifteenth week of pregnancy and CVS is usually performed in the tenth and twelfth weeks of pregnancy.

Craniosynostosis may be visible by fetal ultrasound. Conditions caused by mutations in the FGFR genes account for only a small portion of craniosynostosis. Therefore, assuming that the fetus does not have a family history of one of these conditions, genetic testing for the FGFR genes is unlikely to provide useful additional information.

Treatment and management

Children with Pfeiffer syndrome usually see a team of medical specialists at regular intervals. This team typically includes plastic surgeons, neurosurgeons, orthopedists, ear, nose, and throat doctors (otolaryngologists), dentists, and other specialists. The affected person may see the specialists all at once in a craniofacial clinic at a hospital. Many physical problems must be addressed. Developmental, psychosocial, and financial issues are additional concerns. Unfortunately, treatment is aimed at the symptoms, not the underlying cause. Even if craniosynostosis is discovered prenatally, only the symptoms can be treated.

Multiple surgeries are usually performed to progressively correct the craniosynostosis and to normalize facial appearance. A team of surgeons is often involved, including a neurosurgeon and a specialized plastic surgeon. The timing and order of surgeries vary. Patients with syndromic craniosynostosis often require surgery earlier than patients with nonsyndromic craniosynostosis. The first surgery is usually performed early in the first year of life, even in the first few months.

Additional surgeries may be performed for other physical problems. Limb abnormalities often are not correctable. If the limb malformations do not lead to a loss of function, surgery is usually not required. Fixation of the elbow joints may be partially corrected, or at least altered to enable better functioning.

Hydrocephalus, airway obstruction, hearing loss, incomplete eyelid closure, and spine abnormalities require immediate medical attention.

Prognosis

The prognosis for an individual is based on the symptoms he or she has. Individuals with Pfeiffer syndrome type 1 have a better prognosis than individuals with types 2 or 3. But the designation of type is based on that person's symptoms.

Although people with Pfeiffer syndrome may not obtain a completely normal appearance, significant improvement is possible. Timing the surgeries correctly is an important factor in whether they are successful and whether repeat surgeries are required.

Although Pfeiffer syndrome is rare, craniosynostosis is relatively common. Multiple agencies and organizations exist to help families face the challenges of having

a child with craniosynostosis and facial differences. The identification of the FGFR genes that cause Pfeiffer (and other) craniosynostosis syndromes has promoted research into the underlying process that causes Pfeiffer syndrome. It will be another enormous challenge to go from understanding the process to treating the process. But better understanding is a big first step. Also, when the process that causes Pfeiffer and related conditions is better understood, a much clearer knowledge of human development in general will be established.

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American Cleft Palate-Craniofacial Association. 104 South Estes Dr., Suite 204, Chapel Hill, NC 27514. (919) 993-9044. Fax: (919) 933-9604. <http://www.cleftline.org>.

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

Craniosynostosis and Parents Support, Inc. (CAPS). 1136 Iris Lane, Beaufont, SC 29906. (877) 686-CAPS. <http://www.CAPS2000.org>.

FACES: The National Craniofacial Association. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

Headlines: the Craniofacial Support Group. <http://www.headlines.org.uk>.

Let's Face It. PO Box 29972, Bellingham, WA 98228-1972. (360) 676-7325. letsfaceit@faceit.org. <http://www.faceit.org/letsfaceit>.

World Craniofacial Foundation. PO Box 515838, 7777 Forest Lane, Ste C-621, Dallas, TX 75251-5838. (972) 566-6669 or (800) 533-3315. worldcf@worldnet.att.net. <http://www.worldcf.org>.

WEBSITES

Craniofacial Anomalies. Fact Sheet. Pediatric Surgery, Columbia University. <http://cpmcnet.columbia.edu/dept/nsg/PNS/Craniofacial.html>.

Pfeiffer Syndrome Fact Sheet. FACES. <http://www.faces-cranio.org/>.

OTHER

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Michelle Queneau Bosworth, MS, CGC

Pharmacogenetics

Definition

Pharmacogenetics is one of the newest subspecialties of genetics that deals with the relationship between inherited genes and the ability of the body to metabolize drugs.

Description

Medicine today relies on the use of therapeutic drugs to treat disease, but one of the longstanding problems has been the documented variation in patient response to drug therapy. The "recommended" dosage is usually established at a level shown to be effective in 50% of a test population, and based on the patient's initial response, the dosage may be increased, decreased, or discontinued. In rare situations, the patient may experience an adverse reaction to the drug and be shown to have a pharmacogenetic disorder. The unique feature of this group of diseases is that the problem does not occur until after the drug is given, so a person may have a pharmacogenetic defect and never know it if the specific drug required to trigger the reaction is never administered.

Adverse reactions

Consider the case of a 35-year-old male who is scheduled for surgical repair of a hernia. The patient is otherwise in excellent health and has no family history of any serious medical problems. After entering the operating theater, an inhalation anesthetic and/or muscle relaxant is administered to render the patient unconscious. Unexpectedly, there is a significant increase in body temperature, and the patient experiences sustained muscle contraction. If this condition is not reversed promptly, it can lead to death. Anesthesiologists are now very familiar with this type of reaction. It occurs only rarely, but it uniquely identifies the patient as having **malignant**

hyperthermia, a rare autosomal dominant disorder that affects the body's ability to respond normally to anesthetics. Once diagnosed with malignant hyperthermia, it is quite easy to avoid future episodes by simply using a different type of anesthetic when surgery is necessary, but it often takes one negative, and potentially life-threatening, experience to know the condition exists.

An incident that occurred in the 1950s further shows the diversity of pharmacogenetic disorders. During the Korean War, service personnel were deployed in a region of the world where they were at increased risk for malaria. To reduce the likelihood of acquiring that disease, the antimalarial drug primaquine was administered prophylactically. Shortly thereafter, approximately 10% of the African-American servicemen were diagnosed with acute anemia and a smaller percentage of soldiers of Mediterranean ancestry showed a more severe hemolytic anemia. Investigation revealed that the affected individuals had a mutation in the glucose 6-phosphate dehydrogenase (G6PD) **gene**. Functional G6PD is important in the maintenance of a balance between oxidized and reduced molecules in the cells, and, under normal circumstances, a mutation that eliminates the normal enzyme function can be compensated for by other cellular processes. However, mutation carriers are compromised when their cells are stressed, such as when the primaquine is administered. The system becomes overloaded, and the result is oxidative damage of the red blood cells and anemia. Clearly, both the medics who administered the primaquine and the men who took the drug were unaware of the potential consequences. Fortunately, once the drug treatment was discontinued, the individuals recovered.

Research efforts

Drugs are essential to modern medical practice, but, as in the cases of malignant hyperthermia and G6PD deficiency, it has become clear that not all individuals respond equally to each drug. Reactions can vary from positive improvement in the quality of life to life threatening episodes. Annually, in the United States, there are over two million reported cases of adverse drug reactions and a further 100,000 deaths per year as a result of drug treatments. The **Human Genome Project** and other research endeavors are now providing information that is allowing a better understanding of the underlying causes of pharmacogenetic anomalies with the hope that eventually the number of negative episodes can be reduced.

In particular, research on one enzyme family is beginning to revolutionize the concepts of drug therapy. The cytochrome P450 system is a group of related enzymes that are key components in the metabolic conversion of over 50% of all currently used drugs. Studies involving one member of this family, CYP2D6, have revealed the presence of several polymorphic genetic variations (poor, intermediate, extensive, and ultra) that result in different clinical phenotypes with respect to drug metabolism. For example, a poor metabolizer has difficulty converting the therapeutic drug into a useable form, so the unmodified chemical will accumulate in the body and may cause a toxic overdose. To prevent this from happening, the prescribed dosage of the drug must be reduced.

An ultra metabolizer, on the other hand, shows exceedingly rapid breakdown of the drug to the point that the substance may be destroyed so quickly that therapeutic levels may not be reached, and the patient may therefore never show any benefit from treatment. In these cases, switching to another type of drug that is not associated with CYP2D6 metabolism may prove more beneficial.

The third phenotypic class, the extensive metabolizers, is less extreme than the ultra metabolism category, but nevertheless presents a relatively rapid turnover of drug that may require a higher than normal dosage to maintain a proper level within the cells. And, finally, the intermediate phenotype falls between the poor and extensive categories and gives reasonable metabolism and turnover of the drug. This is the group for whom most "recommended" drug dosages appear to be appropriate.

However, the elucidation of the four different metabolic classes has clearly shown that the usual "one size fits all" recommended drug dose is not appropriate for all individuals. In the future, it will become increasingly necessary to know the patient's metabolic phenotype with respect to the drug being given to determine the most appropriate regimen of therapy for that individual.

Future applications

At the present time, pharmacogenetics is still in its infancy with its full potential yet to be realized. Based on current studies, it is possible to envision many different applications in the future. In addition to providing patient-specific drug therapies, pharmacogenetics will aid in the clinician's ability to predict adverse reactions before they occur and identify the potential for drug addiction or overdose. New tests will be developed to monitor the effects of drugs, and new medications will be found that will specifically target a particular genetic abnormality. Increased knowledge in this field should provide a better understanding of the metabolic effects of food additives, work related chemicals, and industrial by-products. In time, these advances will improve the practice of medicine and become the standard of care.

Constance K. Stein, PhD

Phenotype *see* **Genotypes and phenotypes**

Phenylketonuria

Definition

Phenylketonuria (PKU) can be defined as a rare metabolic disorder caused by a deficiency in the production of the hepatic (liver) enzyme phenylalanine hydroxylase (PAH). PKU is the most serious form of a class of diseases referred to as "hyperphenylalaninemia," all of which involve above normal (elevated) levels of phenylalanine in the blood. The primary symptom of untreated PKU, mental retardation, is the result of consuming foods that contain the amino acid phenylalanine, which is toxic to brain tissue.

PKU is an inherited, autosomal recessive disorder. It is the most common genetic disease involving amino acid metabolism. PKU is incurable, but early, effective treatment can prevent the development of serious mental incapacity.

Description

PKU is a disease caused by the liver's inability to produce a particular type of PAH enzyme. This enzyme converts (metabolizes) the amino acid called phenylalanine into another amino acid, tyrosine. This is the only role of PAH in the body. A lack of PAH results in the build-up of abnormally high phenylalanine concentrations (or levels) in the blood and brain. Above normal levels of phenylalanine are toxic to the cells that make up the nervous system and causes irreversible abnormalities in brain structure and function in PKU patients. Phenylalanine is a type of **teratogen**. Teratogens are any substance or organism that can cause birth disorders in a developing fetus.

The liver is the body's chief protein processing center. Proteins are one of the major food nutrients. They are generally very large molecules composed of strings of smaller building blocks or molecules called amino acids. About twenty amino acids exist in nature. The body breaks down proteins from food into individual amino acids and then reassembles them into "human" proteins. Proteins are needed for growth and repair of cells and tissues, and are the key components of enzymes, antibodies, and other essential substances.

PKU and the human nervous system

The extensive network of nerves in the brain and the rest of the nervous system are made up of nerve cells. Nerve cells have specialized extensions called dendrites and axons. Stimulating a nerve cell triggers nerve impulses, or signals, that speed down the axon. These nerve impulses then stimulate the end of an axon to release chemicals called neurotransmitters that spread out and communicate with the dendrites of neighboring nerve cells.

Many nerve cells have long, wire-like axons that are covered by an insulating layer called the myelin sheath. This covering helps speed nerve impulses along the axon. In untreated PKU patients, abnormally high phenylalanine levels in the blood and brain can produce nerve cells with abnormal axons and dendrites, and cause imperfections in the myelin sheath referred to as hypomyelination and demyelenation. This loss of myelin can "short circuit" nerve impulses (messages) and interrupt cell communication. A number of brain scan studies also indicate a degeneration of the white matter in the brains of older patients who have not maintained adequate dietary control.

PKU can also affect the production of one of the major neurotransmitters in the brain, called dopamine. The brain makes dopamine from the amino acid tyrosine. PKU patients who do not consume enough tyrosine in their diet cannot produce sufficient amounts of dopamine. Low dopamine levels in the brain disrupt normal communication between nerve cells, which results in impaired cognitive (mental) function.

Some preliminary research suggests that nerve cells of PKU patients also have difficulty absorbing tyrosine. This abnormality may explain why many PKU patients who receive sufficient dietary tyrosine still experience some form of learning disability.

Behavior and academic performance

IQ (intelligence quotient) tests provide a measure of cognitive function. The IQ of PKU patients is generally lower than the IQ of their healthy peers. Students with PKU often find academic tasks difficult and must struggle harder to succeed than their non-PKU peers. They may require special tutoring and need to repeat some of their courses. Even patients undergoing treatment programs may experience problems with typical academic tasks such as math, reading, and spelling. Visual perception, visual-motor skills, and critical thinking skills can also be affected. Ten years of age seems to be an important milestone for PKU patients. After age 10, variations in a patient's diet seems to have less influence on their IQ development.

People with PKU tend to avoid contact with others, appear anxious, and show signs of **depression**. However, some patients may be much more expressive and tend to

KEY TERMS

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are "essential amino acids" which the body cannot make and must therefore be obtained from food).

Axon—Skinny, wire-like extension of nerve cells.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genetic disease—A disease that is (partly or completely) the result of the abnormal function or expression of a gene; a disease caused by the inheritance and expression of a genetic mutation.

IQ—Abbreviation for Intelligence Quotient. Compares an individual's mental age to his/her true or chronological age and multiplies that ratio by 100.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system, which help them conduct impulses more quickly.

Nervous system—The complete network of nerves, sense organs, and brain in the body.

Phenylalanine—An essential amino acid that must be obtained from food since the human body cannot manufacture it.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

have hyperactive, talkative, and impulsive personalities. It is also interesting to note that people with PKU are less likely to display such habits as lying, teasing, and active disobedience. It should be emphasized that current research findings are still quite preliminary and more extensive research is needed to clearly show how abnormal phenylalanine levels in the blood and brain might affect behavior and academic performance.

Genetic profile

PKU symptoms are caused by alterations or mutations in the genetic code for the PAH enzyme. Mutations in the PAH **gene** prevent the liver from producing adequate levels of the PAH enzyme needed to break down phenylalanine. The PAH gene and its PKU mutations are found on chromosome 12 in the human genome. In more detail, PKU mutations can involve many different types of changes, such as deletions and insertions, in the **DNA** of the gene that codes for the PAH enzyme.

PKU is described as an inherited, autosomal recessive disorder. The term autosomal means that the gene for PKU is not located on either the X or Y sex chromosome. The normal PAH gene is dominant to recessive PKU mutations. A recessive genetic trait, such as PKU, is one that is expressed—or shows up—only when two copies are inherited (one from each parent).

A person with one normal and one PKU gene is called a carrier. A carrier does not display any symptoms of the disease because their liver produces normal quantities of the PAH enzyme. However, PKU carriers can pass the PKU genetic mutation onto their children. Two carrier parents have a 25% chance of producing a baby with PKU symptoms, and a 50% chance having a baby that is a carrier for the disease. Although PKU conforms to these basic genetic patterns of **inheritance**, the actual expression, or phenotype, of the disease is not strictly an "either/or" situation. This is because there are at least 400 different types of PKU mutations. Although some PKU mutations cause rather mild forms of the disease, others can initiate much more severe symptoms in untreated individuals. The more severe the PKU mutation, the greater the effect on cognitive development and performance (mental ability).

Also, it must be remembered that human cells contain two copies of each type of gene. Different combinations of any two PKU mutations tend to produce a wide spectrum of physiological and psychological symptoms. For example, patients who receive two "severe" PKU mutations from their parents can potentially develop more serious symptoms than people who possess a combination of one severe type and one milder form of mutation. To further complicate the genetic picture of PKU,

other types of genes have been identified which seem to be responsible for the abnormal processing of phenylalanine in brain tissue. These abnormalities add to the severity of PKU symptoms experienced by patients who inherit these genes. In more detail, the association of multiple types of genes with a single condition, such as PKU, is referred to as molecular heterogeneity.

Demographics

One in 50 individuals in the United States have inherited a gene for PKU. About five million Americans are PKU carriers. About one in 15,000 babies test positive for PKU in the United States. Studies indicate that the incidence of this disease in Caucasian and Native American populations is higher than in African-American, Hispanic, and Asian populations.

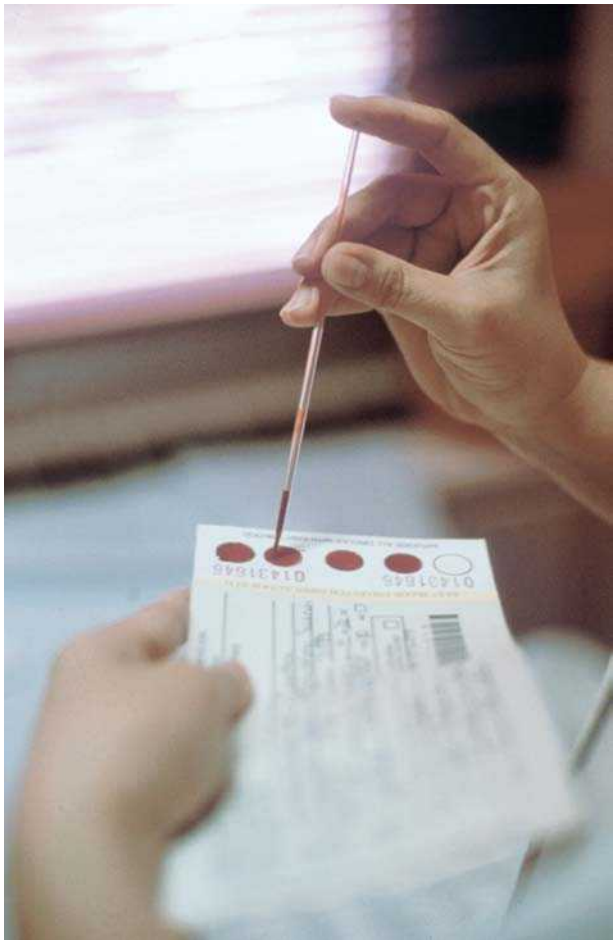
Signs and symptoms

Untreated PKU patients develop a broad range of symptoms related to severely impaired cognitive function, sometimes referred to as mental retardation. Other symptoms can include extreme patterns of behavior, delayed speech development, seizures, a characteristic body odor, and light body pigmentation. The light pigmentation is due to a lack of melanin, which normally colors the hair, skin, and eyes. Melanin is made from the amino acid tyrosine, which is lacking in untreated cases of PKU. Physiologically, PKU patients show high levels of phenylalanine and low levels of tyrosine in the blood. Babies do not show any visible symptoms of the disease for the first few months of life. However, typical PKU symptoms usually do show up by a baby's first birthday.

Diagnosis

The primary diagnostic test for PKU is the measurement of phenylalanine levels in a drop of blood taken from the heel of a newborn baby's foot. This screening procedure is referred to as the Guthrie test (Guthrie bacterial inhibition assay). In this test, PKU is confirmed by the appearance of bacteria growing around high concentrations of phenylalanine in the blood spot. PKU testing was introduced in the early 1960s and is the largest genetic screening program in the United States. It is required by law in all 50 states. Early diagnosis is critical. It ensures the early treatment PKU babies need to develop normally and avoid the complications of PKU.

The American Academy of Pediatrics recommends that this test be performed on infants between 24 hours and seven days after birth. The preferred time for testing is after the baby's first feeding. If the initial PKU test produces a positive result, then follow-up tests are performed to confirm the diagnosis and to determine if the elevated phenylalanine levels may be caused by some medical condition other than PKU. Treatment for PKU is recommended for babies that show a blood phenylalanine level of 7–10 mg/dL or higher for more than a few consecutive days. Another, more accurate test procedure for PKU measures the ratio (comparison) of the amount of phenylalanine to the amount of tyrosine in the blood.



A technician is performing a test to screen for PKU. *(Custom Medical Stock Photo, Inc.)*

Newer diagnostic procedures (called mutation analysis and genotype determination) can actually identify the specific types of PAH gene mutations inherited by PKU infants. Large-scale studies have helped to clarify how various mutations affect the ability of patients to process phenylalanine. This information can help doctors develop more effective customized treatment plans for each of their PKU patients.

Treatment and management

The severity of the PKU symptoms experienced by people with this disease is determined by both lifestyle

and genetic factors. In the early 1950s, researchers first demonstrated that phenylalanine-restricted diets could eliminate most of the typical PKU symptoms—except for mental retardation. Today, dietary therapy (also called nutrition therapy) is the most common form of treatment for PKU patients. PKU patients who receive early and consistent dietary therapy can develop fairly normal mental capacity to within about five IQ points of their healthy peers. By comparison, untreated PKU patients generally have IQ scores below 50.

Infants with PKU should be put on a specialized diet as soon as they are diagnosed to avoid progressive brain damage and other problems caused by an accumulation of phenylalanine in the body. A PKU diet helps patients maintain very low blood levels of phenylalanine by restricting the intake of natural foods that contain this amino acid. Even breast milk is a problem for PKU babies. Special PKU dietary mixtures or formulas are usually obtained from medical clinics or pharmacies.

Phenylalanine is actually an essential amino acid. This means that it has to be obtained from food because the body cannot produce this substance on its own. Typical diets prescribed for PKU patients provide very small amounts of phenylalanine and higher quantities of other amino acids, including tyrosine. The amount of allowable phenylalanine can be increased slightly as a child becomes older.

In addition, PKU diets include all the nutrients normally required for good health and normal growth, such as carbohydrates, fats, vitamins, and minerals. High protein foods like meat, fish, chicken, eggs, nuts, beans, milk, and other dairy products are banned from PKU diets. Small amounts of moderate protein foods (such as grains and potatoes) and low protein foods (some fruits and vegetables, low protein breads and pastas) are allowed. Sugar-free foods, such as diet soda, which contain the artificial sweetener aspartame, are also prohibited foods for patients with PKU. That is because aspartame contains the amino acid phenylalanine.

Ideally, school-age children with PKU should be taught to assume responsibility for managing their diet, recording food intake, and for performing simple blood tests to monitor their phenylalanine levels. Blood tests should be done in the early morning when phenylalanine levels are highest. Infants and young children require more frequent blood tests than older children and adults. The amount of natural foods allowed in a diet could be adjusted to ensure that the level of phenylalanine in the blood is kept within a safe range—two to 6 mg/dL before 12 years of age and 2–15 mg/dL for PKU patients over 12 years old.

A specialized PKU diet can cause abnormal fluctuations in tyrosine levels throughout the day. Thus, some health professionals recommend adding time released tyrosine that can provide a more constant supply of this amino acid to the body. It should be noted that some PKU patients show signs of learning disabilities even with a special diet containing extra tyrosine. Research studies suggest that these patients may not be able to process tyrosine normally.

For PKU caregivers, providing a diet that is appealing as well as healthy and nutritious is a constant challenge. Many patients with PKU, especially teenagers, find it difficult to stick to the relatively bland PKU diet for extended periods of time. Some older patients decide to go off their diet plan simply because they feel healthy. However, many patients who abandon careful nutritional management develop cognitive problems, such as difficulties remembering, maintaining focus, and paying attention. Many PKU health professionals contend that all patients with PKU should adhere to a strictly controlled diet for life.

One promising line of PKU research involves the synthesis (manufacturing) of a new type of enzyme that can break down phenylalanine in food consumed by the patient. This medication would be taken orally and could prevent the absorption of digested phenylalanine into the patient's bloodstream.

In general, medical researchers express concern about the great variation in treatment programs currently available to PKU patients around the world. They have highlighted the urgent need for new, consistent international standards for proper management of PKU patients, which should emphasize comprehensive psychological as well as physiological monitoring and assessment.

PKU and Pregnancy

Women with PKU must be especially careful with their diets if they want to have children. They should ensure that phenylalanine blood levels are under control before conception and throughout pregnancy. Mothers with elevated (higher than normal) phenylalanine levels are high risk for having babies with significant birth disorders, such as microencephaly (smaller than normal head size), and congenital heart disease (abnormal heart structure and function), stunted growth, mental impairment, and psychomotor (coordination) difficulties. This condition is referred to as maternal PKU and can even affect babies who do not have the PKU disease.

Prognosis

Early newborn screening, careful monitoring, and a life-long strict dietary management can help PKU patients to live normal, healthy, and long lives.

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American Academy of Allergy, Asthma & Immunology. 611 E. Wells St, Milwaukee, WI 53202. (414) 272-6071. Fax: (414) 272-6070. <http://www.aaaai.org/default.stm>.

Centers for Disease Control. GDP Office, 4770 Buford Highway NE, Atlanta, GA 30341-3724. (770) 488-3235. <http://www.cdc.gov/genetics>.

Children's PKU Network. 1520 State St., Suite 111, San Diego, CA 92101-2930. (619) 233-3202. Fax: (619) 233 0838. pkunetwork@aol.com.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National PKU News. Virginia Schuett, editor/dietician. 6869 Woodlawn Avenue NE #116, Seattle, WA 98115-5469. (206) 525-8140. Fax: (206) 525-5023. <http://www.pkunews.org>.

University of Washington PKU Clinic. CHDD, Box 357920, University of Washington, Seattle, WA. (206) 685-3015. Within Washington State: (877) 685-3015. Clinic Coordinator: vam@u.washington.edu. <http://depts.washington.edu/pku/contact.html.>.

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Marshall G. Letcher, MA

Phocomelia *see* **Roberts SC phocomelia**

Phytanic acid oxidase deficiency *see* **Refsum disease**

Phytanic acid storage disease *see* **Infantile refsum disease**

Pierre-Robin sequence

Definition

Pierre-Robin Sequence consists of the micrognathia, (small lower jaw), or retrognathia (lower jaw displaced to

KEY TERMS

Endoscopy—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

Fibroid—A non-cancerous tumor of connective tissue made of elongated, threadlike structures, or fibers, which usually grow slowly and are contained within an irregular shape. Fibroids are firm in consistency but may become painful if they start to break down or apply pressure to areas within the body. They frequently occur in the uterus and are generally left alone unless growing rapidly or causing other problems. Surgery is needed to remove fibroids.

Uterus—A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

the back), glossoptosis (displacement of the tongue into the throat) and obstruction of the airway. It is usually accompanied by a cleft palate (an opening in the roof of the mouth). The term sequence is used to describe the pattern of multiple anomalies derived from a single known prior anomaly or mechanical factor.

Description

Children born with Pierre-Robin sequence are found to have small mandibles (lower jaws), or mandibles that are displaced back, tongues that are pushed back into the throat, and difficulty breathing of varying degrees. They also have difficulty feeding. Pierre-Robin sequence is usually accompanied by a cleft palate. It is also known as Pierre-Robin syndrome.

Genetic profile

Pierre-Robin sequence can occur in association with other syndromes; isolated (not associated with other malformations); or in associations with other developmental disorders that do not represent a specific syndrome. Heredity has not been proven to be a factor in the cause of isolated Pierre-Robin sequence. Pierre-Robin sequence found in association with numerous syndromes may have a mode of **inheritance** that is related to the syndrome itself. The mode of inheritance includes single **gene** as well as **chromosomal abnormalities**.

The cause of the abnormal lower jaw in Pierre-Robin syndrome may be mechanical, genetic, teratogenic, or multi-factorial. Mechanical factors such as fibroids inside the uterus may constrict the lower jaw preventing it from growing. Single gene or chromosomal abnormalities produce syndromes that have Pierre-Robin sequence. Teratogenic (anything that affects development of the embryo) causes include maternal use of alcohol. Multi-factorial inheritance means that the cause is a combination of environmental and hereditary factors.

Demographics

The incidence of Pierre-Robin sequence is reported to be one out of 8,500 live births. Other reports show that the range is one out of 2,000 to one out of 50,000 live births. This wide range is due to different diagnostic criteria and the presence or absence of associated syndromes. Fewer than 20% of newborns born with Pierre-Robin sequence have the isolated type.

Signs and symptoms

In Pierre-Robin sequence, the lower jaw of the fetus displaces the tongue backwards into the throat. The tongue located in this abnormal position blocks the embryonic structures from joining in the midline in order to form the palate, the roof of the mouth. The result is a cleft palate, which is an opening in the roof of the mouth. The size of the cleft palate varies as well as its position. It is not present in all patients.

Babies born with Pierre-Robin have difficulty feeding and breathing because the tongue—pushed backwards by the lower jaw—obstructs the throat. Feeding and breathing difficulties may be very mild or very severe.

Affected persons may also develop hearing problems due to fluid collecting in the ears.

Diagnosis

Prenatal ultrasonic examination may show findings to indicate the possibility of Pierre-Robin sequence alerting the physician to be prepared at birth for the possibility of the baby having breathing and feeding problems.

Treatment and management

The type of treatment varies according to the severity of the symptoms and their duration. Babies may not require any therapy if they have no symptoms of breathing difficulties and no feeding difficulties

If breathing difficulties are mild, the easiest management is keeping the baby in the prone position. This position causes the tongue to fall forward, relieving the obstruction. A thorough evaluation of these patients must

be conducted, which includes endoscopy of the airways and upper digestive tract. Close monitoring must be maintained because the prone position may obscure breathing difficulties.

If positioning the patient prone fails, a nasopharyngeal airway may be used but only for a short time. The airway is a tube passed through the nose into the upper airway, which the baby can breath through.

If the above methods fail or are required for a prolonged length of time, then some type of surgical intervention will be required. Surgical procedures include glossopexy, in which the tongue is sutured to the lower lip in order to prevent it from moving back into the throat causing obstruction. Subperiosteal release of the floor of the mouth muscles on the lower jaw is an operation in which the tongue can no longer move back into the throat because muscles are released from their insertions. Tracheotomy is performed by surgically cutting an opening in the trachea (windpipe). This opening bypasses the obstruction. The choice of surgical intervention varies according to the duration and severity of respiratory obstruction; other causes of respiratory obstruction that may be present; and the experience of the surgeon. Glossopexy and tracheotomy are temporary and reversed when the baby can breath adequately on its own.

The treatment of feeding difficulty varies according to the degree of difficulty. It has been found that the severity of feeding difficulty is proportional to the severity of airway obstruction. Feeding is usually accomplished with specialized cleft palate nipples and bottles or nasogastric tubes (a feeding tube passed through the nose and into the stomach). Sometimes a gastrotomy tube is needed for feeding. This is a tube passed through a surgical opening made in the abdominal wall and stomach.

Children with Pierre-Robin sequence are prone to hearing loss due to fluid collecting behind the tympanic membrane (ear drum), and may require drainage tubes placed into the ear.

If the child has a cleft palate, it is usually surgically repaired between the ages of nine and 18 months.

Prognosis

The prognosis for individuals with Pierre-Robin sequence varies with the severity of symptoms and if it is associated with other congenital abnormalities. The more severe the symptoms and associated congenital abnormalities, the greater the risk of complications.

The rate at which the lower jaw starts to catch up in growth depends on the cause of Pierre-Robin sequence. The majority of children with the isolated type will achieve near normal jaw size within a few years of birth. If Pierre-Robin sequence is part of a syndrome that has a small jaw, the jaw may remain small throughout life.

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Let's Face It. Box 29972, Bellingham, WA 98228-1972. (360) 676-7325. letsfaceit@faceit.org. <http://www.faceit.org//>.

WEBSITES

About Face International. <http://aboutfaceinternational.org/>.

Pierre Robin Network. <http://www.pierrerobin.org>.

Farris F. Gulli, MD

Pierre-Robin syndrome *see* **Pierre-Robin sequence**

Pierre-Robin syndrome with fetal chrondrodysplasia *see* **Weissenbacher-Zweymuller syndrome**

Pituitary dwarfism

Definition

Dwarfism is a condition in which the growth of the individual is very slow or delayed. There are many forms of dwarfism. The word pituitary is in reference to the pituitary gland in the body. This gland regulates certain chemicals (hormones) in the body. Therefore, pituitary dwarfism is decreased bodily growth due to hormonal problems. The end result is a proportionate little person, because the height as well as the growth of all other structures of the individual are decreased.

Description

Pituitary dwarfism is caused by problems arising in the pituitary gland. The pituitary gland is also called the hypophysis. The pituitary gland is divided into two halves: the anterior (front) and posterior (back) halves. The anterior half produces six hormones: growth hormone, adrenocorticotropin (corticotropin), thyroid stimulating homone (thyrotropin), prolactin, follicle stimulating hormone, and lutenizing hormone. The posterior pituitary gland only produces two hormones. It produces antidiuretic hormone (vasopressin) and oxytocin.

Most forms of dwarfism are a result of decreased production of hormones from the anterior half of the pituitary gland. The most common form is due to decreases of growth hormone which will be discussed here. These decreases during childhood cause the individual's arms, legs, and other structures to develop normal proportions for their bodies, but at a decreased rate.

When all of the hormones of the anterior pituitary gland are not produced, this is called panhypopituitarism. Another type of dwarfism occurs when only the growth hormone is decreased. Dwarfism can also result from a lack of somatomedin C (also called insulin like growth factor, IGF-1) production. Somatomedin C is a hormone produced in the liver that increases bone growth when growth hormone is present. The African pygmy and the Levi-Lorain dwarfs lack the ability to produce somatomedin C in response to growth hormone. All causes of dwarfism lead to a proportionate little person.

Growth is the body's response to different hormones. The forebrain contains a small organ called the hypothalamus, which is responsible for releasing hormones in response to the body's needs for purposes of regulation. Growth hormone is produced in the anterior pituitary gland when growth hormone-releasing hormone (GHRH), is released by the hypothalamus. Growth hormone is then released and stimulates the liver to produce IGF-1. In return, IGF-1 stimulates the long bones to grow in length. Thus, growth can be slowed down or stopped if there is a problem making any of these hormones or if there is a problem with the cells receiving these hormones.

KEY TERMS

Adrenocorticotropin (corticotrophin)—A hormone that acts on cells of the adrenal cortex, causing them to produce male sex hormones and hormones that control water and mineral balance in the body.

Antidiuretic hormone (vasopressin)—A hormone that acts on the kidneys to regulate water balance.

Craniopharyngioma—A tumor near the pituitary gland in the craniopharyngeal canal that often results in intracranial pressure.

Deprivational dwarfism—A condition where emotional disturbances are associated with growth failure and abnormalities of pituitary function.

Follicle-stimulating hormone (FSH)—A hormone that in females stimulates estrogen and in males stimulates sperm production.

Growth hormone—A hormone that eventually stimulates growth. Also called somatotropin.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Lutenizing hormone—A hormone secreted by the pituitary gland that regulates the menstrual cycle and triggers ovulation in females. In males it stimulates the testes to produce testosterone.

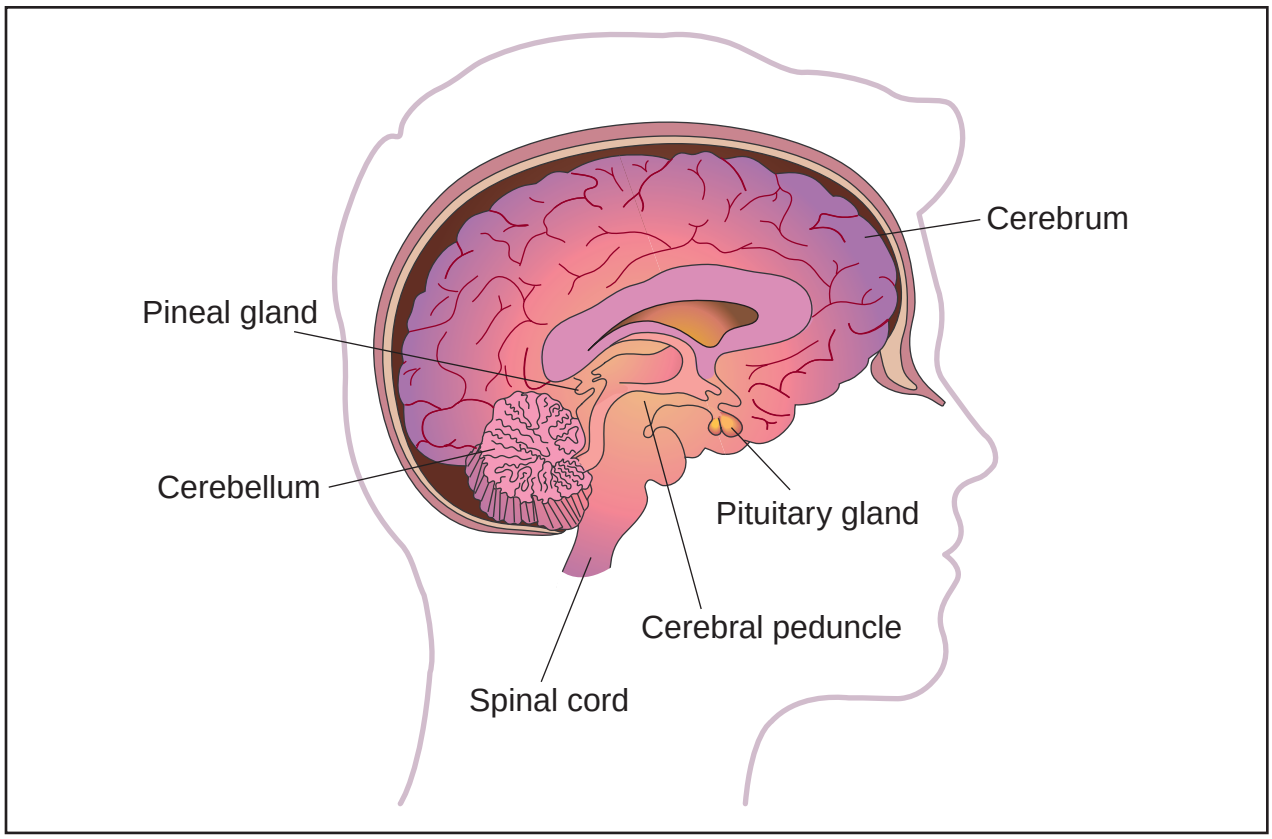
Oxytocin—A hormone that stimulates the uterus to contract during child birth and the breasts to release milk.

Panhypopituitarism—Generalized decrease of all of the anterior pituitary hormones.

Prolactin—A hormone that helps the breast prepare for milk production during pregnancy.

Puberty—Point in development when the gonads begin to function and secondary sexual characteristics begin to appear.

Thyroid stimulating hormone (thyrotropin)—A hormone that stimulates the thyroid gland to produce hormones that regulate metabolism.



(Gale Group)

Genetic profile

Pituitary dwarfism has been shown to run in families. New investigations are underway to determine the specific cause and location of the **gene** responsible for dwarfism. The human cell contains 46 **chromosomes** arranged in 23 pairs. Most of the genes in the two chromosomes of each pair are identical or almost identical with each other. However, with dwarfism, there appears to be disruption on different areas of chromosome 3 and 7. Some studies have isolated defects for the production of pituitary hormones to the short arm (the "p" end) of chromosome 3 at a specific location of 3p11. Other studies have found changes on the short arm of chromosome 7.

Demographics

Some estimates show that there are between 10,000 and 15,000 children in the United States who have growth problems due to a deficiency of growth hormone.

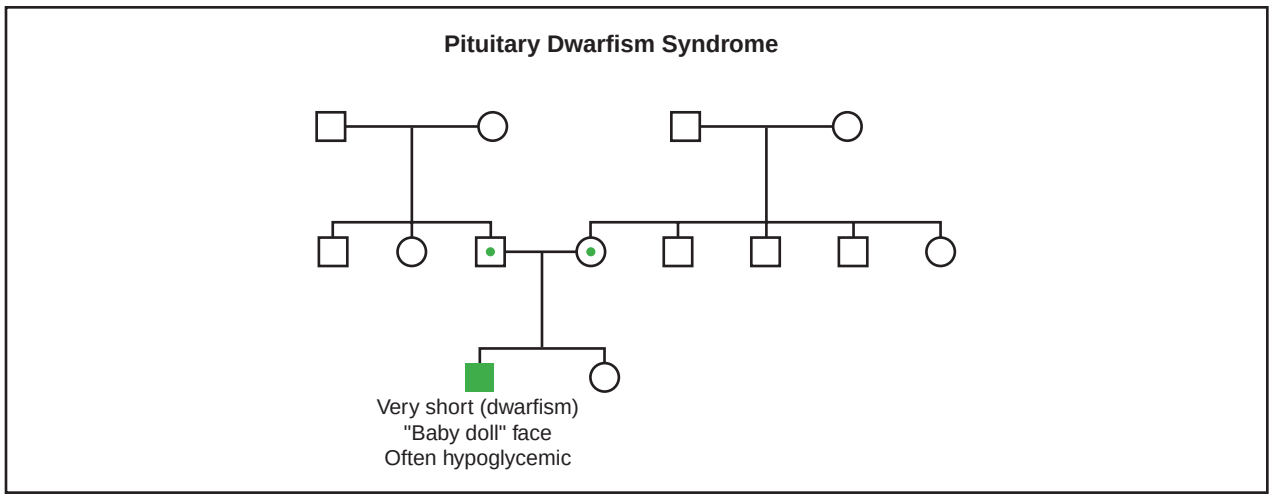
Signs and symptoms

A child with a growth hormone deficiency is often small with an immature face and chubby body build. The child's growth will slow down and not follow the normal growth curve patterns. In cases of tumor, most commonly craniopharyngioma (a tumor near the pituitary gland), children and adolescents may present with neurological symptoms such as headaches, vomiting, and problems with vision. The patient may also have symptoms of double vision. Symptoms such as truly bizarre and excessive drinking behaviors (polydipsia) and sleep disturbances may be common.

Diagnosis

The primary symptom of pituitary dwarfism is lack of height. Therefore, a change in the individual's growth habits will help lead to a diagnosis. Another diagnostic technique uses an x ray of the child's hand to determine the child's bone age by comparing this to the child's actual chronological age. The bone age in affected children is usually two years or more behind the chronological age. This means that if a child is ten years old, his or her bones will look like they are those of an eight-year-old child. The levels of growth hormone and somatomedin C must also be measured with blood tests.

Hypopituitarism may be gained or acquired following birth for several reasons. It could be due to trauma to



(Gale Group)

the pituitary gland such as a fall or following surgery to the brain for removal of a tumor. It may also be due to the child's environment (deprivational dwarfism).

On examination by the doctor there may be optic nerve atrophy, if the dwarfism is due to a type of tumor. X rays of the area where the pituitary gland is located (sella turcica) or more advanced imaging such as magnetic resonance imaging (MRI) or computed tomography (CT) may show changes of the pituitary gland itself. Computed tomography is an advanced form of x ray that will help determine the integrity of the bone and how much calcification the tumor is producing. Magnetic resonance imaging, will also help in the diagnosis. MRI is a type of imaging device that can visualize soft tissues such as muscle and fat.

If the dwarfism is due to environmental and emotional problems, the individual may be hospitalized to monitor hormone levels. Following a few days of hospitalization, hormone levels may become normal due to avoidance of the original environment.

Treatment and management

The main course of therapy is growth hormone replacement therapy when there is lack of growth hormone in the body. A pediatric endocrinologist, a doctor specializing in the hormones of children, usually administers this type of therapy before a child's growth plates have fused or joined together. Once the growth plates have fused, GH replacement therapy is rarely effective.

Growth hormone used to be collected from recently deceased humans. However, frequent disease complications resulting from human growth hormone collected from deceased bodies lead to the banning of this method. In the mid-1980s, techniques were discovered that could produce growth hormones in the lab. Now, the only growth hormone used for treatment is that made in a laboratory.

A careful balancing of all of the hormones produced by the pituitary gland is necessary for patients with panhypopituitarism. This form of dwarfism is very difficult to manage.

Prognosis

The prognosis for each type of dwarfism varies. A panhypopituitarism dwarf does not pass through the initial onset of adult sexual development (puberty) and never produces enough gonadotropic hormones to develop adult sexual function. These individuals also have a great deal of other medical conditions. Dwarfism due to only growth hormone deficiency has a different prognosis. These individuals do pass through puberty and mature sexually, however, they remain proportionately small in stature.

If the individual is lacking only growth hormone then growth hormone replacement therapy can be administered. The success of treatment with growth hormone varies however. An increase in height of 4–6 in (10–15 cm) can occur in the first year of treatment. Following this first year, the response to the hormone is not as successful. Therefore the amount of growth hormone administered must be tripled to maintain this rate. Long-term use is considered successful if the individual grows at least 0.75 in (2 cm) per year more than they would without the hormone. However, if the growth hormone treatment is not administered before the long bones—such as the legs and arms—fuse, then the individual will never grow. This fusion is completed by adult age.

Improvement for individuals with dwarfism due to other causes such as a tumor, varies greatly. If the dwarfism is due to deprevational causes, then removing that child from that environment should help to alleviate the problem.

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Human Growth Foundation. 997 Glen Cove Ave., Glen Head, NY 11545. (800) 451-6434. Fax: (516) 671-4055. <http://www.hgf1@hgfound.org>.

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408. (806) 737-8186 or (888) LPA-2001. lpadatabase@juno.com. <http://www.lpaonline.org>.

MAGIC Foundation for Children's Growth. 1327 N. Harlem Ave., Oak Park, IL 60302. (708) 383-0808 or (800) 362-4423. Fax: (708) 383-0899. mary@magicfoundation.org. <http://www.magicfoundation.org/ghd.html>.

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Jason S. Schliesser, DC

PK deficiency *see* **Pyruvate kinase deficiency**

PKD *see* **Polycystic kidney disease**

PKU *see* **Phenylketonuria**

Poland anomaly

Definition

Poland anomaly is a rare pattern of malformations present at birth that includes unilateral changes in the chest and shoulder girdle muscles, forearm bones, and fingers. Although there are other associated features, the most recognized characteristics are abnormalities of the major chest muscles (pectoralis) and the presence of syndactyly or webbing that joins the fingers of the hand. Treatment of this anomaly is mainly through reconstructive surgery.

Description

Poland anomaly (also known as Poland syndactyly, Poland syndrome, Poland sequence, or Pectoral dysplasia-dysdactyly) was first described in 1841 by Alfred Poland, who was a medical student at Guy's Hospital in London when he noted malformations in the body of a deceased convict named George Elt. Today, the diagnosis of Poland anomaly may encompass various combinations of the following abnormalities:

- Absence of major chest muscles: pectoralis major, pectoralis minor.
- Hand anomalies: syndactyly (webbed or fused fingers), shortened fingers.
- Underdeveloped forearm bones: ulna, radius.
- Underdeveloped or absence of the nipple and, in females, the breast.
- Absence of groups of rib cartilage.

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Dextrocardia—Defect in which the position of the heart is the mirror image of its normal position.

Pectoralis muscles—Major muscles of the chest wall.

Renal agenesis—Absence or failure of one or both kidneys to develop normally.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Syndactyly—Webbing or fusion between the fingers or toes.

- Absence of shoulder girdle muscles: latissimus dorsi, serratus anterior.
- Underdeveloped skin and underlying tissue of the chest.
- Abnormal curvature of the spine.
- Patchy hair growth under the arm.
- Rare associations with abnormalities in the heart, kidney, or development of certain cancers.

In most cases, physical abnormalities are confined to one side of the body and tend to favor the right side by almost two to one. The manifestations of Poland anomaly are extremely variable and rarely are all the features recognized in one individual. Involvement of the pectoralis muscle and fingers is the most consistent feature.

The exact cause of Poland anomaly is not known, but may result from the interruption of fetal growth at about the 46th day of pregnancy, when the fetal fingers and pectoralis muscle are developing. Several researchers have suggested that there may be too little blood flow through the fetal subclavian artery that goes to the chest and arm; the more severe the blood flow disruption, the more numerous and severe the resulting malformations. However, the final proof for this idea has not been found.

Genetic profile

Most occurrences of Poland anomaly appear to be sporadic (i.e., random, and not associated with a inherited disorder) and are not passed on from parent to child. However, there have been rare reports of Poland anomaly that appear in multiple members of the same family. In at least one case, this familial occurrence of Poland anomaly appears to be inherited in an autosomal dominant pattern. The fact that other organs systems (kidney, heart) and increased risks of certain cancers are associated with this condition supports the hypothesis that there may be some genetic abnormality. However, if there is some sort of genetic or inherited cause in some patients with Poland anomaly, it has not been identified. For purposes of **genetic counseling**, the Poland anomaly can be regarded as a sporadic condition with an extremely low risk of being transmitted from parent to child.

Demographics

Poland anomaly is not common. It affects one child in about 20,000 to 30,000. Geographically, estimates of the frequency range from one in 17,213 in Japanese school children, to an average of one in 32,000 live births in British Columbia, with a low incidence of one in 52,530, in Hungary. For reasons that are unclear, Poland anomaly is three times more frequent in boys than girls.

Signs and symptoms

The manifestations of Poland anomaly are most often limited to the physical manifestations described above. The degree to which this condition is disabling depends on which manifestations are present and their individual severity, but most often relate to disabilities in the affected arm and hand. Upon rare occasions, the Poland anomaly is associated with dextrocardia (in which the position of the heart is the mirror image of its normal position), renal agenesis (maldevelopment of the kidney) or the association with cancers such as leukemia, leiomyosarcoma, and non-Hodgkin lymphoma. Intelligence is not impaired by Poland anomaly.

Diagnosis

The diagnosis of Poland anomaly relies on physical exam and radiographic evaluation, such as the use of x rays or other imaging techniques to define abnormal or missing structures that are consistent with the criteria for Poland anomaly, as described above. There is no laboratory blood or genetic test that can be used to identify people with Poland anomaly.

Treatment and management

During early development and progressing through until young adulthood, children with Poland anomaly should be educated and trained in behavioral and mechanical methods to adapt to their disabilities. This program is usually initiated and overseen by a team of health care professionals including a pediatrician, physical therapist, and occupational therapist. A counselor

specially trained to deal with issues of disabilities in children is often helpful in assessing problem areas and encouraging healthy development of self-esteem. Support groups and community organizations for people with Poland anomaly or other disabilities often prove useful as well.

After growth development is advanced enough (usually late adolescence or early adulthood), reconstructive plastic surgery may be offered, primarily to correct cosmetic appearance. The goal of reconstruction is to restore the natural contour of the chest wall while stabilizing the chest wall defect. Chest wall reconstruction must be tailored to the requirements of each patient, but often involves moving and grafting ribs and muscles from other parts of the body to reconstruct the chest wall and breast. In addition, bioengineered cartilage or breast implants can be used to help give the chest a more normal appearance. Hand abnormalities are treated according to the severity, and requires individual consultation with a reconstructive plastic surgeon.

Prognosis

The prognosis for people with Poland anomaly is excellent. Reconstructive surgery is safe and cosmetic corrections achieved can be significant. Associated symptoms of heart and kidney defects as well as **cancer** association are rare, but indicate that patients with Poland anomaly should be followed closely by a physician familiar with the condition.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Oren Traub, MD, PhD

Poland syndactyly *see* **Poland anomaly**

Poland syndrome *see* **Poland anomaly**

Polycystic kidney disease

Definition

Polycystic kidney disease (PKD) is one of the most common of all life-threatening human **genetic disorders**. It is an incurable genetic disorder characterized by the formation of fluid-filled cysts in the kidneys of affected individuals. These cysts multiply over time. It was originally believed that the cysts eventually caused kidney failure by crowding out the healthy kidney tissue. It is now thought that the kidney damage seen in PKD is actually the result of the body's immune system. The immune system, in its attempts to rid the kidney of the cysts, instead progressively destroys the formerly healthy kidney tissue.

Description

A healthy kidney is about the same size as a human fist. PKD cysts, which can be as small as the head of a pin or as large as a grapefruit, can expand the kidneys until each one is bigger than a football and weighs as much as 38 lbs (17 kg).

There are two types of PKD: infantile PKD, which generally shows symptoms prior to birth; and adult onset PKD. Individuals affected with infantile PKD are often stillborn. Among the liveborn individuals affected with infantile PKD, very few of these children survive to the age of two. The adult onset form of PKD is much more common. The time and degree of symptom onset in the adult form of PKD can vary widely, even within a single family with two or more affected individuals. Symptoms of this form of PKD usually start to appear between the ages of 20 and 50. Organ deterioration progresses more slowly in adult onset PKD than it does in the infantile form; but, if left untreated, adult onset PKD also eventually leads to kidney failure.

Genetic profile

Polycystic kidney disease is expressed as both a recessive and a dominant trait. A recessive genetic trait will not cause disease in a child unless it it inheritied from both parents. A dominant genetic trait can be inherited from just one parent. Those people affected with autosomal dominant PKD (ADPKD) have the much more common adult onset form. Those with autosomal recessive PKD (ARPKD) have the infantile form.

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Cancer—A disease caused by uncontrolled growth of the body's cells.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Diuretics—Medications that increase the excretion of urine.

Kidney—Either of two organs in the lumbar region that filter the blood, excreting the end products of the body's metabolism in the form of urine and regulating the concentrations of hydrogen, sodium, potassium, phosphate and other ions in the body.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Ultrasonogram—A procedure where high-frequency sound waves that cannot be heard by human ears are bounced off internal organs and tissues. These sound waves produce a pattern of echoes, which are then used by the computer to create sonograms or pictures of areas inside the body.

Uremic poisoning—Accumulation of waste products in the body.

There are mutations on at least three genes that cause adult onset PKD. Approximately 85% of these cases are known to arise from mutations in the PKD1 **gene** that has been mapped to a region on the short arm of chromosome 16 (16p13.3-p13.12). Another 10–15% of cases of adult onset PKD are thought to be caused by mutations in the PKD2 gene that has been mapped to a region on the long arm of chromosome 4 (4q21-q23). As of early 2001, it is thought that the remainder of the cases of PKD are caused by mutations in the PKD3 gene, which has not yet been mapped. This unidentified "PKD3 gene" may, in fact, be more than one gene.

Adult onset PKD is transmitted from parents to their offspring as a non-sex linked (autosomal) dominant trait. This means that if either parent carries this genetic mutation, there is a 50% chance that their child will inherit this disease. In the case of two affected parents, there is a 75% probability that their children will be affected with adult onset PKD.

Infantile PKD is caused by a non-sex linked (autosomal) recessive genetic mutation that has been mapped to a region on the short arm of chromosome 6 (6p21). Both parents must be carriers of this mutation for their children to be affected with infantile PKD. In the case of two carrier parents, the probability is 25% that their child will be affected by infantile PKD.

Demographics

One of the most common of all life-threatening genetic diseases, PKD affects more than 60,000 Americans. Over 12.5 million people worldwide are affected with PKD. Approximately one in every 400 to 1000 people is affected with ADPKD. Another one in 10,000 are affected with ARPKD. PKD is observed in both males and females. PKD is also observed with equal probability among ethnic groups.

Signs and symptoms

A baby born with infantile PKD has floppy, low-set ears, a pointed nose, a small chin, and folds of skin surrounding the eyes (epicanthal folds). Large, rigid masses can be felt on the back of both thighs (flanks), and the baby usually has trouble breathing.

In the early stages of adult onset PKD, many people show no symptoms. Generally, the first symptoms to develop are: high blood pressure (hypertension); general fatigue; pain in the lower back or the backs of the thighs; headaches; and/or urinary tract infections accompanied by frequent urination.

As PKD becomes more advanced, the kidneys' inability to function properly becomes more pronounced. The cysts on the kidney may begin to rupture and the kidneys tend to be much larger than normal. Individuals affected with PKD have a much higher rate of kidney stones than the rest of the population at this, and later stages, of the disease. Approximately 60% of those individuals affected with PKD develop cysts in the liver, while 10% develop cysts in the pancreas.

Because the kidneys are primarily responsible for cleaning the blood, individuals affected with PKD often have problems involving the circulatory system. These include: an underproduction of red blood cells which results in an insufficient supply of oxygen to the tissues and organs (anemia); an enlarged heart (cardiac hyper-

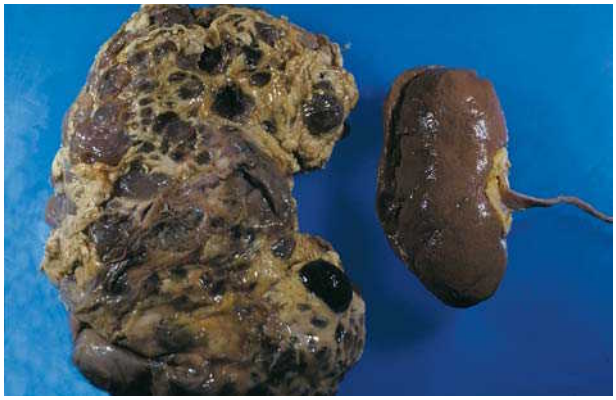
trophy) probably caused by long term hypertension; and a leakage of the valve between the left chambers (auricle and ventricle) of the heart (mitral valve prolapse). Less common (affecting approximately 5% of PKD patients) are brain aneurysms. An aneurysm is an abnormal and localized bulging of the wall of a blood vessel. If an aneurysm within the brain leaks or bursts, it may cause a stroke or even death.

Other health problems associated with adult onset PKD include: chronic leg or back pain; frequent infections; and, herniations of the groin and abdomen, including herniation of the colon (diverticular disease). A herniation, or hernia, is caused when a tissue, designed to hold the shape of an underlying tissue, becomes weakened at a particular spot. The underlying tissue pushes against this weakened area until the area is no longer able to hold back the underlying tissue and the area forms an abnormal bulge through which the underlying tissue projects. Diverticular disease is caused by a weakening of the muscles that hold the shape of the organs of the digestive tract. These muscles weaken allowing these organs, particularly one section of the colon, to form sac-like projections that can trap feces and become infected, or rupture.

In the final stages of PKD, the major symptom is kidney (renal) failure. **Renal failure** is indicated by an increase of nitrogen (in the form of urea) in the blood (uremia, or uremic poisoning). Uremia is a rapidly fatal condition without treatment.

Diagnosis

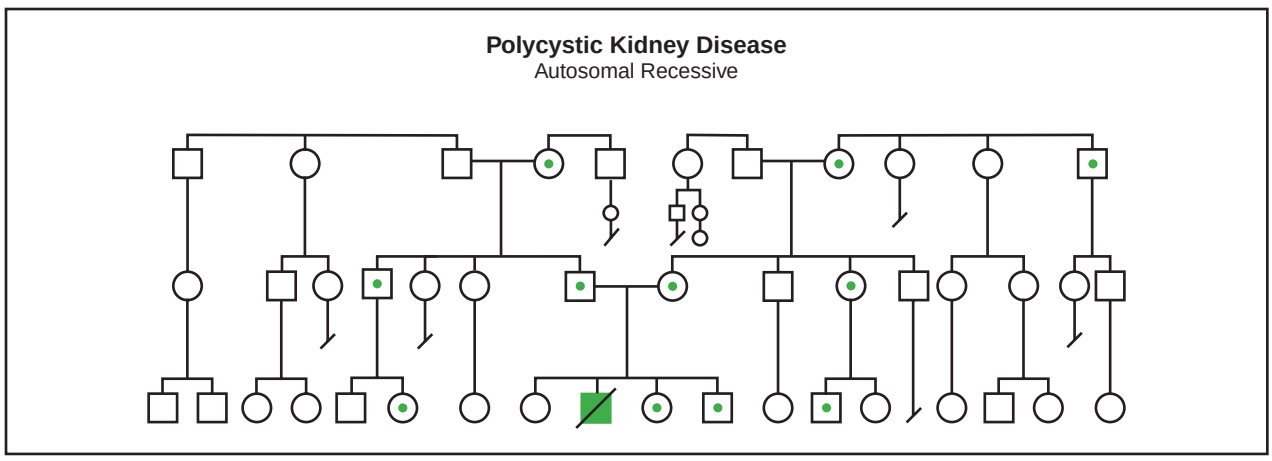
Many patients who have PKD do not have any symptoms. Their condition may not be discovered unless tests that detect it are performed for other reasons.



The cyst covered kidney on the left is substantially larger than the normal kidney on the right. *(Photo Researchers, Inc.)*

When symptoms of PKD are present, the diagnostic procedure begins with a family medical history and physical examination of the patient. If several family members have PKD, there is a strong likelihood that the patient has it too. If the disease is advanced, the doctor will be able to feel the patient's enlarged kidneys. Heart murmur, high blood pressure, and other signs of cardiac impairment can also be detected.

Urinalysis and a blood test called creatine clearance can indicate how effectively the kidneys are functioning. Scanning procedures using intravenous dye reveal kidney enlargement or deformity and scarring caused by cysts. Ultrasound and computed tomography scans (CT scans) can reveal kidney enlargement and the cysts that caused it. CT scans can highlight cyst-damaged areas of the kidneys. A sampling of the kidney cells (biopsy) may be performed to verify the diagnosis.



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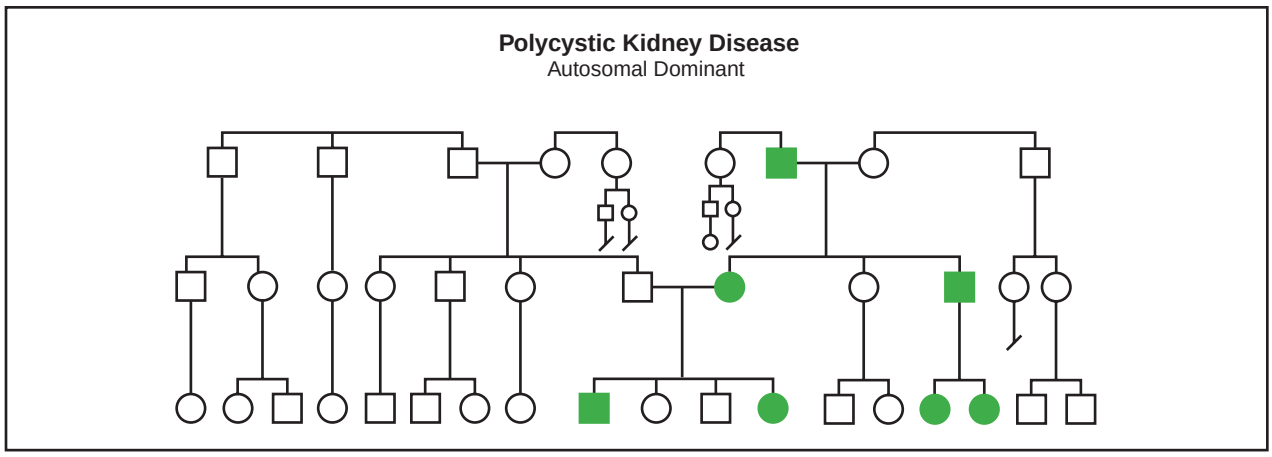

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Treatment and management

There is no way to prevent cysts from forming or becoming enlarged, or to prevent PKD from progressing to kidney failure. Treatment goals include preserving healthy kidney tissue; controlling symptoms; and preventing infection and other complications.

If adult PKD is diagnosed before symptoms become evident, urinalysis and other diagnostic tests are performed at six-week intervals to monitor the patient's health status. If results indicate the presence of infection or another PKD-related health problem, aggressive antibiotic therapy is initiated to prevent inflammation that can accelerate disease progression; iron supplements or infusion of red blood cells are used to treat anemia; and surgery may be needed to drain cysts that bleed, cause pain, have become infected, or interfere with normal kidney function.

Lowering high blood pressure can slow loss of kidney function. Blood-pressure control, which is the cornerstone of PKD treatment, is difficult to achieve. Therapy may include anti-hypertensive medications, diuretic medications, and/or a low-salt diet. As kidney function declines, some patients need dialysis and/or a kidney transplant.

There is no known way to prevent PKD, but certain lifestyle modifications can help control symptoms. People who have PKD should not drink heavily or smoke. They should not use aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), or other prescription or over-the-counter medications that can impair kidney function. Individuals affected with PKD should eat a balanced diet, exercise regularly, and maintain a weight appropriate for their height, age, and body type. Regular medical monitoring is also recommended.

Prognosis

There is no known cure for PKD. Those affected with infantile PKD generally die before the age of two. In adults, untreated disease can be rapidly fatal or continue to progress slowly, even after symptoms of kidney failure appear. About half of all adults with PKD also develop kidney failure. Unless the patient undergoes dialysis or has a kidney transplant, they usually do not survive more than four years after diagnosis.

Although medical treatment can temporarily alleviate symptoms of PKD, the expanding cysts continue to increase pressure on the kidneys. Kidney failure and uremic poisoning (accumulation of waste products the body is unable to eliminate) generally cause death about 10 years after symptoms first appear.

Medications used to fight **cancer** and reduce elevated cholesterol levels have slowed the advance of PKD in laboratory animals. They may soon be used to treat adults and children who have the disease. Researchers are also evaluating the potential benefits of anti-inflammatory drugs, which may prevent the scarring that destroys kidney function.

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Paul A. Johnson

Polycystic ovary syndrome

Definition

Polycystic ovary syndrome (PCOS), formerly Stein-Leventhal syndrome, is a disorder in which women do not experience normal release of eggs from the ovaries, they have an abnormal production of male hormones, and their body is resistant to the effects of the hormone insulin. The disorder results in infertility, abnormal masculinization, and increased risk of developing heart disease and certain cancers.

Description

The normal function of the female reproductive system is complex, requiring the interplay of different organ systems. One set of important organs are the ovaries. The ovaries are two small structures contained in the lower abdomen, on either side of the uterus, that contain small immature eggs, called ova. Ova are stored within the ovaries in individual structures called follicles.

In a monthly cycle, a part of the brain called the pituitary gland secretes two substances into the blood stream—lutenizing hormone (LH) and follicle-stimulating hormone (FSH). As certain levels of LH and FSH build in the blood stream, the follicles of the eggs begin to swell and grow, creating cysts. Eventually, the changing levels of LH and FSH cause one of the ovarian cysts to burst open, releasing a mature egg. This process by which an egg is released from the ovary is called ovulation.

Once a mature egg is released from the ovary, it passes into the fallopian tubes, tube-like structures that are passageways to the uterus. If sperm cells from the male are present within the fallopian tubes, they will join with the egg in a process called fertilization. The fertilized egg can then pass into the uterus and implant into the thickened wall of the uterus where it can develop into a fetus. If no sperm cells are present, the mature egg goes unfertilized and is lost, along with the thickened later of the uterus, in a monthly process called menstruation.

Polycystic ovary syndrome (PCOS), first described by I. F. Stein and M. L. Leventhal in 1935, is a disorder in which normal ovulation does not occur. The term "polycystic" derives from the fact that the egg-containing cysts in the ovaries do not burst open, resulting in enlarged ovaries containing many swelled cysts. The reason for this problem in ovulation is unclear, however several abnormalities have been characterized in women with PCOS. First, there is a disturbance in the production of LH and FSH by the pituitary, leading to altered levels of the substances in the blood stream. There is also evidence that the ovaries do not respond appropriately to the FH and LSH that is present. Second, there is an abnormal over-production of male hormones, called androgens, by the ovaries and the adrenal gland. Finally, women with PCOS are resistant to the effects of the hormone, insulin. Insulin is a hormone made in the pancreas that is responsible for transport of sugar from the blood into the cells. While these abnormalities have been well characterized, it is unclear whether they cause PCOS, or whether they are a result the disease.

Genetic profile

Women diagnosed with PCOS frequently have relatives with symptoms similar to that seen in the disorder. As a result of these observations, many scientists have proposed that genetic factors play a role in the disease. Over the past few decades, researchers have identified families in which PCOS appears to be inherited with an autosomal dominant or an X-linked pattern. However, these cases are rare and do not hold true for the majority of people with PCOS.

Current theories suggest that different genetic changes may result in PCOS or that multiple genetic factors are needed for the full manifestation of the disease. Abnormalities in several genes have been associated with PCOS, including mutations in the genes for follistatin (locus 5p14), 17-beta-hydroxysteroid dehydrogenase (locus 9p22), and a cytochrome P450 enzyme (locus 15q23-q24). Each of these genes plays a different role in the response to LH and FSH, or in the conversion of male hormones to female hormones, although their relationship to PCOS is unclear. Ongoing research is likely to identify further genetic mutations that are associated with PCOS.

KEY TERMS

Acanthosis nigricans—A skin condition characterized by darkly pigmented areas of velvety wart-like growths. Acanthosis nigricans usually affects the skin of the armpits, neck, and groin.

Androgens—A group of steroid hormones that stumulate the development of male sex organs and male secondary sexual characteristics.

Diabetes—An inability to control the levels of sugar in the blood due to an abnormality in the production of, or response to, the hormone insulin.

Fallopian tube—Either of a pair of tubes that conduct ova from the ovaries to the uterus.

Follicle—A pouch-like depression.

Follicle-stimulating hormone (FSH)—A hormone that stimulates estrogen in females and stimulates sperm production in males.

Hirsuitism—The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Infertility—Inability in a woman to become pregnant.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Lutenizing hormone (LH)—A hormone secreted by the pituitary gland that regulates the menstrual cycle and triggers ovulation in females. In males it stimulates the testes to produce testosterone.

Masculinization—Development of excess body and facial hair, deepening of the voice, and increase in muscle bulk in a female due to a hormone disorder.

Menstruation—Discharge of blood and fragments of the uterine wall from the vagina in a monthly cycle in the absence of pregnancy.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Ova—Another name for the egg cells that are located in the ovaries.

Ovary—The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

Ovulation—The monthly process by which an ovarian follicle or cyst ruptures, releasing a mature egg cell.

Pituitary gland—A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicl-stimulating hormone (FSH).

Uterus—A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

Demographics

Estimates of the prevalence of PCOS in the general population have ranged from 2-20% with recent studies suggesting that 3-6% of women of reproductive age are affected by the disorder. This makes PCOS one of the most common hormone disorders in women of reproductive age.

It is unclear whether this disease is distributed uniformly among different geographical areas and ethnic groups, however, studies performed in 1999 show the prevalence of this disorder in the United States is just over 3% in African-American females and almost 5% in Caucasian females. The prevalence of PCOS in Greek women was shown to be higher, nearly 7%.

Signs and symptoms

The first signs of PCOS tend to manifest at puberty. As a result of the failure to ovulate normally, young women with PCOS may fail to menstruate or menstruate only erratically. A small percentage of women may have normal menstrual cycles. Women affected with PCOS often experience infertility, an inability to become pregnant. Additionally, women with PCOS tend to gain weight, and 70% eventually become obese.

The overproduction of androgens leads to changes in the body that are more typical of male development. For example, approximately 70% of women with PCOS will show hair growth on the face, chest, stomach, and thighs (hirsuitism). Simultaneously, they show thinning of the

hair more typical of male-pattern baldness. Other male characteristics, such as deep voice, acne, and increased sex drive may also be present, and affected women often have decreased breast size.

Women with PCOS do not respond appropriately to the hormone, insulin. As a result, 15% of women with PCOS may develop high levels of sugar in the blood later in life, a condition known as diabetes. Resistance to insulin is also associated with dark, warty skin growths in the groin and armpits, known as acanthosis nigricans.

Untreated PCOS is a risk factor for the development of several dangerous conditions. The hormone abnormalities in PCOS place women at considerable risk for endometrial **cancer** and possibly **breast cancer**. The risk of endometrial cancer is three times higher in women with PCOS than in normal women, and small studies suggest that the risk of breast cancer may by three to four times higher. PCOS also results in increased risk of high blood pressure, diabetes, and high cholesterol, all of which contribute to heart disease and stroke.

Diagnosis

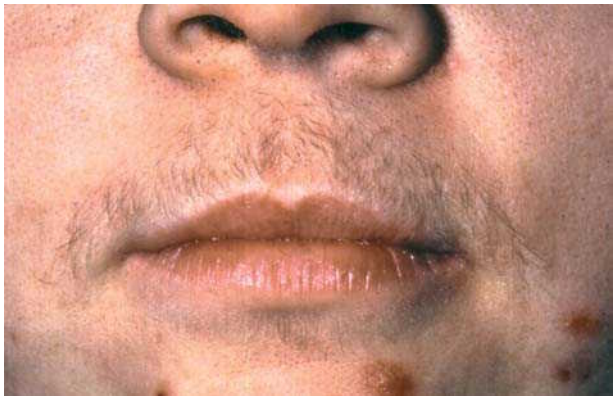
A diagnostic search for PCOS is usually initiated when women experience an absence of menstrual periods for at least six months, an inability to become pregnant, and/or abnormal hair growth or acne. A comprehensive physical exam performed at that time may reveal excessive body hair, low voice, acanthosis nigricans, or obesity. Enlarged ovaries are also identifiable on pelvic examination in about 50% of patients.

Blood tests can be performed that may yield results consistent with PCOS, including abnormal levels of LH and FSH (typically in a ratio of 3:1), abnormally high levels of androgens (testosterone, DHEA, DHEAS), abnormally high levels of insulin, and abnormally low levels of a substance called sex hormone-binding globulin. In addition, a physician may perform a diagnostic test called a "progesterone challenge". In this test, a physician administers a hormone called progesterone to the patient to determine if it will provoke menstruation. If menstruation does occur in response to the progesterone, it is likely that a patient has PCOS.

Finally, an ultrasound examination of the ovaries may be performed to determine if large cystic follicles can be documented. With this approach, the diagnosis of PCOS is based on the finding of more than eight enlarged follicles in the ovary.

Treatment and management

There is no cure for PCOS, thus treatment focuses on several goals, including the restoration of the menstrual cycle, blocking the effect of androgens, reducing insulin resistance, lowering the risk of cancer and heart disease, and possibly restoring ovulation and fertility.



Females affected with Stein-Leventhal syndrome often have excessive facial hair, known as hirsutism. *(Photo Researchers, Inc.)*

In patients who do not desire pregnancy, hormones can be administered in the form of birth control pills, which may result in normal menstrual cycles, decreased hair growth and acne, and a lower risk of developing endometrial cancer. Although women will note a decrease in hair growth after approximately six months of treatment with birth control pills, additional cosmetic hair removal therapy is often necessary. In women who do not respond appropriately to birth control pills, another medication known as luprolide (Lupron) can be used, but with more long term side effects (e.g., hot flushes, bone demineralization, atrophic vaginitis).

Other types of medication can be used to block the effects of androgens. When these medications are taken with birth control pills, 75% of women report decreased body hair growth. The most commonly used medications to block androgen effects are spironolactone (Aldactone), flutamide (Eulexin), and cyproterone (Cyprostat).

Treatment with medications that restore the body's normal response to insulin has been shown to decrease LH and androgen levels. Recent studies have demonstrated that such agents restore the menstrual cycle in 68-95% of patients treated for as short a time as four to six months. One of the most commonly used medications to improve the effects of insulin is metformin (Glucophage).

In patients who are trying to become pregnant, a physician can administer medications that will cause ovulation. The main medication used to induce ovulation is clomiphene citrate (Clomid). Ovulation is successful in approximately 75% of women treated with clomiphene, but only 30-40% of women will successfully become

pregnant. Another medication, follitropin alpha (Gonal-F), has achieved pregnancy rates of 58-82%, but may cause more side effects and frequently results in more than one baby per pregnancy.

Some women who do not respond to medications may undergo surgery to remove portions of the ovary. For reasons that are not completely understood, removal of a portion of the ovary may result in some degree of normal menstrual cycles.

While medications and surgery may provide a degree of symptomatic relief for some women, other simultaneous strategies can increase their benefits. Behavior modifications, including weight reduction, diet, and exercise, are recommended for all women with PCOS. As little as a 7% reduction in body weight can lead to a significant decrease in androgen levels and to the resumption of ovulation in obese women with PCOS. Cosmetic techniques, including electrolysis (destruction of the hair follicle using electricity) and laser therapy, may be used to decrease hair growth. Finally, women should be seen regularly for full physical examinations including pelvic exams to aid in the early detection of ovarian, breast, and uterine cancer and should be managed by an interdisciplinary health care team including a primary care physician, obstetrician/gynecologist and reproductive endocrinologist.

Prognosis

While PCOS is one of the most common hormone disorders in young women, proper diagnosis and treatment has greatly increased the quality of life in these individuals. Roughly half of women with PCOS will be able to achieve pregnancy, and about three-fourths will see reduction in masculine traits such as hair growth with proper medical treatment. Initiation of vigorous exercise and a restricted diet may result in even better outcomes. It should be noted that patients with PCOS are at higher risk of developing diabetes, heart disease, and certain cancers and should be seen regularly by a physician. Barring these developments, lifespan in patients with PCOS is approximately the same as the general population.

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Oren Traub, MD, PhD

Polyps and spots syndrome *see* **Peutz-Jeghers syndrome**

Polysplenia syndrome *see* **Asplenia**

Pompe disease *see* **Acid maltase deficiency**

Porphyrias

Definition

The porphyrias are disorders in which the body produces too much porphyrin and insufficient heme (an iron-containing non-protein portion of the hemoglobin molecule). Porphyrin is a foundation structure for heme and certain enzymes. Excess porphyrins are excreted as waste in the urine and stool. Overproduction and overexcretion of porphyrins causes low, unhealthy levels of heme and certain important enzymes creating various physical symptoms.

Description

Biosynthesis of heme is a multistep process that begins with simple molecules and ends with a large, complex heme molecule. Each step of the chemical pathway is directed by its own task-specific protein, called an enzyme. As a heme precursor molecule moves through each step, an enzyme modifies the precursor in some way. If a precursor molecule is not modified, it cannot proceed to the next step, causing a build-up of that specific precursor.

This situation is the main characteristic of the porphyrias. Owing to a defect in one of the enzymes of the heme biosynthesis pathway, protoporphyrins or porphyrins (heme precursors) are prevented from proceeding

further along the pathway. These precursors accumulate at the stage of the enzyme abnormality causing an array of physical symptoms in an affected person. Specific symptoms depend on the point at which heme biosynthesis is blocked and which precursors accumulate. In general, the porphyrias primarily affect the skin and the nervous system. Symptoms can be debilitating or life threatening in some cases. Porphyria is most commonly an inherited condition. It can also, however, be acquired after exposure to poisonous substances.

Heme

Heme is produced in several tissues in the body, but its primary biosynthesis sites are the liver and bone marrow. Heme synthesis for immature red blood cells, namely the erythroblasts and the reticulocytes, occurs in the bone marrow.

Although production is concentrated in the liver and bone marrow, heme is utilized in various capacities in virtually every tissue in the body. In most cells, heme is a key building block in the construction of factors that oversee metabolism and transport of oxygen and energy. In the liver, heme is a component of several vital enzymes, particularly cytochrome P450. Cytochrome P450 is involved in the metabolism of chemicals, vitamins, fatty acids, and hormones; it is very important in transforming toxic substances into easily excretable materials. In immature red blood cells, heme is the featured component of hemoglobin. Hemoglobin is the red pigment that gives red blood cells their characteristic color and their essential ability to transport oxygen.

Heme biosynthesis

The heme molecule is composed of porphyrin and an iron atom. Much of the heme biosynthesis pathway is dedicated to constructing the porphyrin molecule. Porphyrin is a large molecule shaped like a four-leaf clover. An iron atom is placed at its center point in the last step of heme biosynthesis.

The production of heme may be compared to a factory assembly line. At the start of the line, raw materials are fed into the process. At specific points along the line, an addition or adjustment is made to further development. Once additions and adjustments are complete, the final product rolls off the end of the line.

The heme "assembly line" is an eight-step process, requiring eight different and properly functioning enzymes:

1. delta-aminolevulinic acid synthase
2. delta-aminolevulinic acid dehydratase
3. porphobilogen deaminase
4. uroporphyrinogen III cosynthase
5. uroporphyrinogen decarboxylase
6. coproporphyrinogen oxidase
7. protoporphyrinogen oxidase
8. ferrochelatase

The control of heme biosynthesis is complex. Various chemical signals can trigger increased or decreased production. These signals can affect the enzymes themselves or the production of these enzymes, starting at the genetic level. For example, one point at which heme biosynthesis may be controlled is at the first step. When heme levels are low, greater quantities of delta-aminolevulinic acid (ALA) synthase are produced. As a result, larger quantities of heme precursors are fed into the biosynthesis pathway to step up heme production.

Porphyrias

Under normal circumstances, when heme concentrations are at an appropriate level, precursor production decreases. However, a glitch in the biosynthesis pathway—represented by a defective enzyme—means that heme biosynthesis does not reach completion. Because heme levels remain low, the synthesis pathway continues to churn out precursor molecules in an attempt to correct the heme deficit.

The net effect of this continued production is an abnormal accumulation of precursor molecules and development of some type of porphyria. Each type of porphyria corresponds with a specific enzyme defect and an accumulation of the associated precursor. Although there are eight steps in heme biosynthesis, there are only seven types of porphyrias; a change in ALA synthase activity does not have a corresponding porphyria.

Enzymes involved in heme biosynthesis display subtle, tissue-specific variations; therefore, heme biosynthesis may be impeded in the liver, but normal in the immature red blood cells, or vice versa. Incidence of porphyria varies widely between types and occasionally by geographic location. Although certain porphyrias are more common than others, their greater frequency is only relative to other types. All porphyrias are considered to be rare disorders.

In the past, the porphyrias were divided into two general categories based on the location of the porphyrin production. Porphyrias affecting heme biosynthesis in the liver were referred to as hepatic porphyrias. Porphyrias affecting heme biosynthesis in immature red blood cells were referred to as erythropoietic porphyrias (erythropoiesis is the process through which red blood cells are produced). As of 2001, porphyrias are usually

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Biosynthesis—The manufacture of materials in a biological system.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Erythropoiesis—The process through which new red blood cells are created; it begins in the bone marrow.

Erythropoietic—Referring to the creation of new red blood cells.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hematin—A drug administered intravenously to halt an acute porphyria attack. It causes heme biosynthesis to decrease, preventing the further accumulation of heme precursors.

Heme—The iron-containing molecule in hemoglobin that serves as the site for oxygen binding.

Hemoglobin—Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hepatic—Referring to the liver.

Neuropathy—A condition caused by nerve damage. Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

Porphyrin—A large molecule shaped like a four-leaf clover. Combined with an iron atom, it forms a heme molecule.

Protoporphyrin—A precursor molecule to the porphyrin molecule.

grouped into acute and non-acute types. Acute porphyrias produce severe attacks of pain and neurological effects. Non-acute porphyrias present as chronic diseases.

The acute porphyrias, and the heme biosynthesis steps at which enzyme problems occur, are:

- ALA dehydratase deficiency porphyria (step 2). This porphyria type is very rare. The **inheritance** pattern appears to be autosomal recessive. In autosomal recessively inherited disorders a person must inherit two defective genes, one from each parent. A parent with only one **gene** for an autosomal recessive disorder does not display symptoms of the disease.
- Acute intermittent porphyria (step 3). Acute intermittent porphyria (AIP) is also known as Swedish porphyria, pyrroloporphyria, and intermittent acute porphyria. AIP is inherited as an autosomal dominant trait, which means that only one copy of the abnormal gene needs to be present for the disorder to occur. Simply inheriting this gene, however, does not necessarily mean that a person will develop the disease. Approximately five to 10 per 100,000 persons in the United States carry a gene for AIP, but only 10% of these people ever develop symptoms of the disease.
- Hereditary coproporphyria (step 6). Hereditary coproporphyria (HCP) is inherited in an autosomal dominant manner. As with all porphyrias, it is an uncommon ailment. By 1977, only 111 cases of HCP were recorded; in Denmark, the estimated incidence is two in one million people.
- Variegate porphyria (step 7). Variegate porphyria (VP) is also known as porphyria variegata, protocoproporphyria, South African genetic porphyria, and Royal malady (supposedly King George III of England and Mary, Queen of Scots, had VP). VP is inherited in an autosomal dominant manner and is especially prominent in South Africans of Dutch descent. Among that population, the incidence is approximately three in 1,000 persons. It is estimated that there are 10,000 cases of VP in South Africa. Interestingly, it appears that the affected South Africans are descendants of two Dutch settlers who came to South Africa in 1680. Among other populations, the incidence of VP is estimated to be one to two cases per 100,000 persons.

The non-acute porphyrias, and the steps of heme biosynthesis at which they occur, are:

- Congenital erythropoietic porphyria (step 4). Congenital erythropoietic porphyria (CEP) is also called Gunther's disease, erythropoietic porphyria, congenital porphyria, congenital hematoporphyria, and erythropoietic uroporphyria. CEP is inherited in an autosomal recessive manner. It is a rare disease, esti-

mated to affect less than one in one million people. Onset of dramatic symptoms usually occurs in infancy, but may hold off until adulthood.

- Porphyria cutanea tarda (step 5). Porphyria cutanea tarda (PCT) is also called symptomatic porphyria, porphyria cutanea symptomatica, and idiosyncratic porphyria. PCT may be acquired, typically as a result of disease (especially hepatitis C), drug or alcohol use, or exposure to certain poisons. PCT may also be inherited as an autosomal dominant disorder, however most people remain latent—that is, symptoms never develop. PCT is the most common of the porphyrias, but the incidence of PCT is not well defined.
- Hepatoerythopoietic porphyria (step 5). HEP affects heme biosynthesis in both the liver and the bone marrow. HEP results from a defect in uroporphyrinogen decarboxylase activity (step 5), and is caused by changes in the same gene as PCT. Disease symptoms, however, strongly resemble congenital erythropoietic porphyria. HEP seems to be inherited in an autosomal recessive manner.
- Erythropoietic protoporphyria (step 8). Also known as protoporphyria and erythrohepatic protoporphyria, erythropoietic protoporphyria (EPP) is more common than CEP; more than 300 cases have been reported. In these cases, onset of symptoms typically occurred in childhood.

Causes and symptoms

General characteristics

The underlying cause of all porphyrias is an abnormal enzyme important to the heme biosynthesis pathway. Porphyrias are inheritable conditions. In virtually all cases of porphyria, an inherited factor causes the enzyme's defect. An environmental trigger—such as diet, drugs, or sun exposure—may be necessary before any symptoms develop. In many cases, symptoms never develop. These asymptomatic individuals may be completely unaware that they have a gene for porphyria.

All of the hepatic porphyrias—except porphyria cutanea tarda—follow a pattern of acute attacks separated by periods in which no symptoms are present. For this reason, this group is often referred to as the acute porphyrias. The erythropoietic porphyrias and porphyria cutanea tarda do not follow this pattern and are considered to be chronic conditions.

The specific symptoms of each porphyria vary based on which enzyme is affected and whether that enzyme occurs in the liver or in the bone marrow. The severity of symptoms can vary widely, even within the same type of porphyria. If the porphyria becomes symptomatic, the common factor between all types is an abnormal accumulation of protoporphyrins or porphyrin.

ALA dehydratase porphyria (ADP)

ADP is characterized by a deficiency of ALA dehydratase. ADP is caused by mutations in the delta-aminolevulinate dehydratase gene (ALAD) at 9q34. Of the few cases on record, the prominent symptoms were vomiting, pain in the abdomen, arms, and legs, and neuropathy. (Neuropathy refers to nerve damage that can cause pain, numbness, or paralysis.) The nerve damage associated with ADP could cause breathing impairment or lead to weakness or paralysis of the arms and legs.

Acute intermittent porphyria (AIP)

AIP is caused by a deficiency of porphobilogen deaminase, which occurs due to mutations in the hydroxymethylbilane synthase gene (HMBS) located at 11q23.3. Symptoms of AIP usually do not occur unless a person with the deficiency encounters a trigger substance. Trigger substances can include hormones (for example oral contraceptives, menstruation, pregnancy), drugs, and dietary factors. Most people with this deficiency never develop symptoms.

Attacks occur after puberty and commonly feature severe abdominal pain, nausea, vomiting, and constipation. Muscle weakness and pain in the back, arms, and legs are also typical symptoms. During an attack, the urine is a deep reddish color. The central nervous system may also be involved. Possible psychological symptoms include hallucinations, confusion, seizures, and mood changes.

Congenital erythropoietic porphyria (CEP)

CEP is caused by a deficiency of uroporphyrinogen III cosynthase due to mutations in the uroporphyrinogen III cosynthase gene (UROS) located at 10q25.2-q26.3. Symptoms are often apparent in infancy and include reddish urine and possibly an enlarged spleen. The skin is unusually sensitive to light and blisters easily if exposed to sunlight. (Sunlight induces protoporphyrin changes in the plasma and skin. These altered protoporphyrin molecules can cause skin damage.) Increased hair growth is common. Damage from recurrent blistering and associated skin infections can be severe. In some cases facial features and fingers may be lost to recurrent damage and infection. Deposits of protoporphyrins can sometimes lead to red staining of the teeth and bones.

Porphyria cutanea tarda (PCT)

PCT is caused by deficient uroporphyrinogen decarboxylase. PCT is caused by mutations in the uropor-

phyrinogen decarboxylase gene (UROD) located on chromosome 1 at 1p34. PCT may occur as an acquired or an inherited condition. The acquired form usually does not appear until adulthood. The inherited form may appear in childhood, but often demonstrates no symptoms. Early symptoms include blistering on the hands, face, and arms following minor injuries or exposure to sunlight. Lightening or darkening of the skin may occur along with increased hair growth or loss of hair. Liver function is abnormal but the signs are mild.

Hepatoerythopoietic porphyria (HEP)

HEP is linked to a deficiency of uroporphyrinogen decarboxylase in both the liver and the bone marrow. HEP is an autosomal recessive disease caused by mutations in the gene responsible for PCT, the uroporphyrinogen decarboxylase gene (UROD), located at 1p34. The gene is the shared, but the mutations, inheritance, and specific symptoms of these two diseases are different. The symptoms of HEP resemble those of CEP.

Hereditary coproporphyria (HCP)

HCP is similar to AIP, but the symptoms are typically milder. HCP is caused by a deficiency of coproporphyrinogen oxidase due to mutations in a gene by the same name at 3q12. The greatest difference between HCP and AIP is that people with HCP may have some skin sensitivity to sunlight. However, extensive damage to the skin is rarely seen.

Variegate porphyria (VP)

VP is caused by a deficiency of protoporphyrinogen oxidase. There is scientific evidence that VP is caused by a mutation in the gene for protoporphyrinogen oxidase located at 1q22. Like AIP, symptoms of VP occur only during attacks. Major symptoms of this type of porphyria include neurological problems and sensitivity to light. Areas of the skin that are exposed to sunlight are susceptible to burning, blistering, and scarring.

Erythropoietic protoporphyria (EPP)

Owing to deficient ferrochelatase, the last step in the heme biosynthesis pathway—the insertion of an iron atom into a porphyrin molecule—cannot be completed. This enzyme deficiency is caused by mutations in the ferrochelatase gene (FECH) located at 18q21.3. The major symptoms of this disorder are related to sensitivity to light—including both artificial and natural light sources. Following exposure to light, a person with EPP experiences burning, itching, swelling, and reddening of the skin. Blistering and scarring may occur but are neither common nor severe. EPP is associated with increased risks for gallstones and liver complications. Symptoms can appear in childhood and tend to be more severe during the summer when exposure to sunlight is more likely.

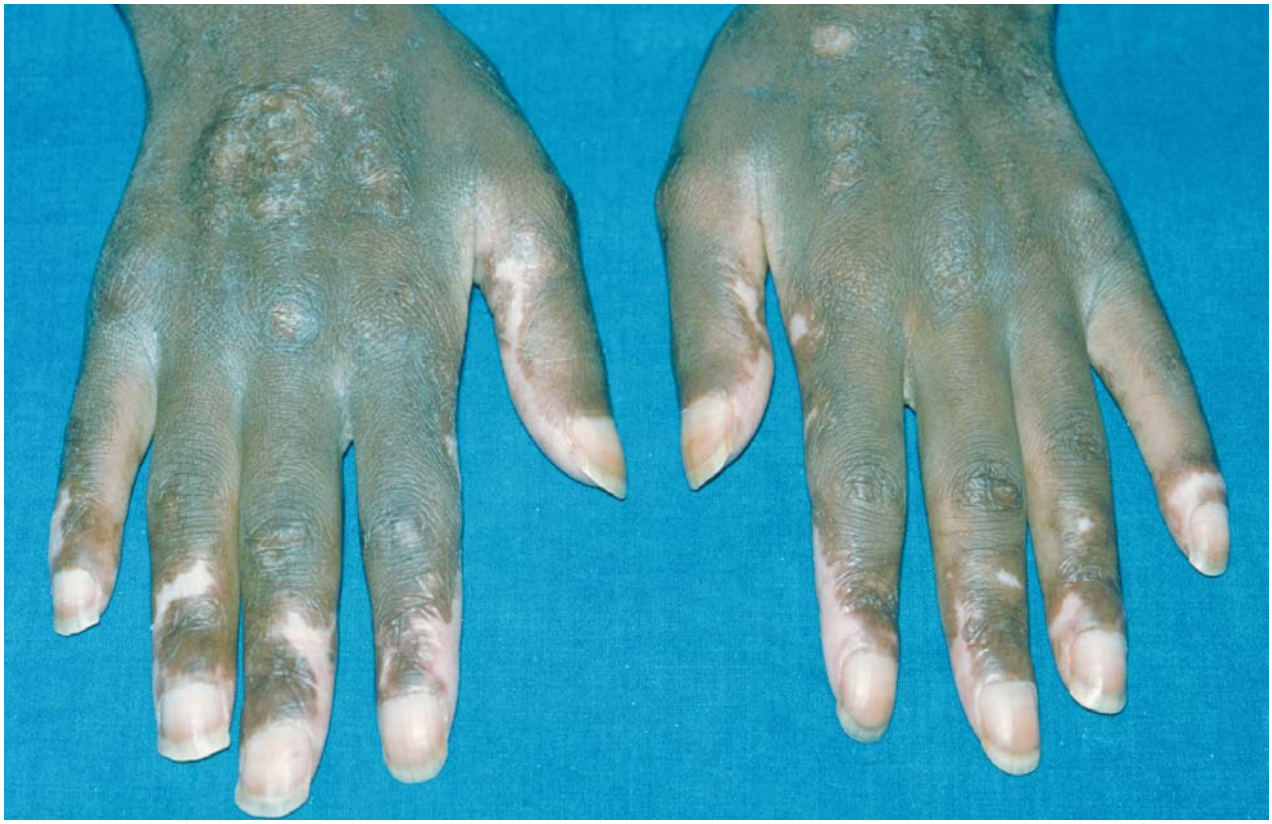
Diagnosis

Depending on the array of symptoms an individual may exhibit, the possibility of porphyria may not immediately come to a physician's mind. In the absence of a family history of porphyria, non-specific symptoms, such as abdominal pain and vomiting, may be attributed to other disorders. Neurological symptoms, including confusion and hallucinations, can lead to an initial suspicion of psychiatric disease. Diagnosis is more easily accomplished in cases in which non-specific symptoms appear in combination with symptoms more specific to porphyria, like neuropathy, sensitivity to sunlight, or certain other manifestations. Certain symptoms, such as urine the color of port wine, are hallmark signs very specific to porphyria. DNA analysis is not yet of routine diagnostic value.

A common initial test measures protoporphyrins in the urine. However, if skin sensitivity to light is a symptom, a blood plasma test is indicated. If these tests reveal abnormal levels of protoporphyrins, further tests are done to measure heme precursor levels in red blood cells and the stool. The presence and estimated quantity of porphyrin and protoporphyrins in biological samples are easily detected using spectrofluorometric testing. Spectrofluorometric testing uses a spectrofluorometer that directs light of a specific strength at a fluid sample. The porphyrins and protoporphyrins in the sample absorb the light energy and fluoresce, or glow. The spectrofluorometer detects and measures fluorescence, which indicates the amount of porphyrins and protoporphyrins in the sample.

Whether heme precursors occur in the blood, urine, or stool gives some indication of the type of porphyria, but more detailed biochemical testing is required to determine their exact identity. Making this determination yields a strong indicator of which enzyme in the heme biosynthesis pathway is defective; which, in turn, allows a diagnosis of the particular type of porphyria.

Biochemical tests rely on the color, chemical properties, and other unique features of each heme precursor. For example, a screening test for acute intermittent porphyria (AIP) is the Watson-Schwartz test. In this test, a special dye is added to a urine sample. If one of two heme precursors—porphobilinogen or urobilinogen—is present, the sample turns pink or red. Further testing is necessary to determine whether the precursor present is porphobilinogen or urobilinogen—only porphobilinogen is indicative of AIP.



Early symptoms of cutaneous porphyrias include blistering on the hands, face, and arms following minor injuries or exposure to sunlight. *(Custom Medical Stock Photo, Inc.)*

Other biochemical tests rely on the fact that heme precursors become less soluble in water (able to be dissolved in water) as they progress further through the heme biosynthesis pathway. For example, to determine whether the Watson-Schwartz urine test is positive for porphobilinogen or urobilinogen, chloroform is added to the test tube. Chloroform is a water-insoluble substance. Even after vigorous mixing, the water and chloroform separate into two distinct layers. Urobilinogen is slightly insoluble in water, while porphobilinogen tends to be water-soluble. The porphobilinogen mixes more readily in water than chloroform, so if the water layer is pink (from the dye added to the urine sample), that indicates the presence of porphobilinogen, and a diagnosis of AIP is probable.

As a final test, measuring specific enzymes and their activities may be done for some types of porphyrias; however, such tests are not done as a screening method. Certain enzymes, such as porphobilinogen deaminase (the abnormal enzyme in AIP), can be easily extracted from red blood cells; other enzymes, however, are less readily collected or tested. Basically, an enzyme test involves adding a certain amount of the enzyme to a test tube that contains the precursor it is supposed to modify. Both the production of modified precursor and the rate at which it appears can be measured using laboratory equipment. If a modified precursor is produced, the test indicates that the enzyme is doing its job. The rate at which the modified precursor is produced can be compared to a standard to measure the efficiency of the enzyme.

Treatment and management

Treatment for porphyria revolves around avoiding acute attacks, limiting potential effects, and treating symptoms. Treatment options vary depending on the specific type of porphyria diagnosed. **Gene therapy** has been successful for both CEP and EPP. In the future, scientists expect development of gene therapy for the remaining porphyrias. Given the rarity of ALA dehydratase porphyria, definitive treatment guidelines for this rare type have not been developed.

Acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria

Treatment for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria follows the same basic regime. A person who has been diagnosed with one of these porphyrias can prevent most attacks by

avoiding precipitating factors, such as certain drugs that have been identified as triggers for acute porphyria attacks. Individuals must maintain adequate nutrition, particularly in respect to carbohydrates. In some cases, an attack can be stopped by increasing carbohydrate consumption or by receiving carbohydrates intravenously.

When attacks occur, prompt medical attention is necessary. Pain is usually severe, and narcotic analgesics are the best option for relief. Phenothiazines can be used to counter nausea, vomiting, and anxiety, and chloral hydrate or diazepam is useful for sedation or to induce sleep. Hematin, a drug administered intravenously, may be used to halt an attack. Hematin seems to work by signaling the pathway of heme biosynthesis to slow production of precursors. Women, who tend to develop symptoms more frequently than men owing to hormonal fluctuations, may find ovulation-inhibiting hormone therapy to be helpful.

Gene therapy is a possible future treatment for these porphyrias. An experimental animal model of AIP has been developed and research is in progress.

Congenital erythropoietic porphyria

The key points of congenital erythropoietic porphyria treatment are avoiding exposure to sunlight and prevention of skin trauma or skin infection. Liberal use of sunscreens and consumption of beta-carotene supplements can provide some protection from sun-induced damage. Medical treatments such as removing the spleen or administering transfusions of red blood cells can create short-term benefits, but these treatments do not offer a cure. Remission can sometimes be achieved after treatment with oral doses of activated charcoal. Severely affected patients may be offered bone marrow transplantation, which appears to confer long-term benefits.

Porphyria cutanea tarda

As with other porphyrias, the first line of defense is avoidance of factors, especially alcohol, that could bring about symptoms. Regular blood withdrawal is a proven therapy for pushing symptoms into remission. If an individual is anemic or cannot have blood drawn for other reasons, chloroquine therapy may be used.

Erythropoietic protoporphyria

Avoiding sunlight, using sunscreens, and taking beta-carotene supplements are typical treatment options for erythropoietic protoporphyria. The drug, cholestyramine, may reduce the skin's sensitivity to sunlight as well as the accumulated heme precursors in the liver. Liver transplantation has been used in cases of liver failure, but it has not effected a long-term cure of the porphyria.

Alternative treatment

Acute porphyria attacks can be life-threatening events, so attempts at self-treatment can be dangerous. Alternative treatments can be useful adjuncts to conventional therapy. For example, some people may find relief for the pain associated with acute intermittent porphyria, hereditary coproporphyria, or variegate porphyria through acupuncture or hypnosis. Relaxation techniques, such as yoga or meditation, may also prove helpful in pain management.

Prognosis

Even when porphyria is inherited, symptom development depends on a variety of factors. In the majority of cases, a person remains asymptomatic throughout life. About one percent of acute attacks can be fatal. Other symptoms may be associated with temporarily debilitating or permanently disfiguring consequences. Measures to avoid these consequences are not always successful, regardless of how diligently they are pursued. Although pregnancy has been known to trigger porphyria attacks, dangers associated with pregnancy as not as great as was once thought.

Prevention

For the most part, the porphyrias are attributed to inherited genes; such inheritance cannot be prevented. However, symptoms can be limited or prevented by avoiding factors that trigger symptom development.

People with a family history of an acute porphyria should be screened for the disease. Even if symptoms are absent, it is useful to know about the presence of the gene to assess the risks of developing the associated porphyria. This knowledge also reveals whether a person's offspring may be at risk. Prenatal testing for certain porphyrias is possible. Prenatal diagnosis of congenital erythropoietic porphyria has been successfully accomplished. Any prenatal tests, however, would not indicate whether a child would develop porphyria symptoms; only that they might have the potential to do so.

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Julia Barrett
Judy Hawkins, MS

Portosystemic venous shunt-congenital *see* **Patent ductus arteriosus**

Potter sequence *see* **Oligohydramnios sequence**

Prader-Willi syndrome

Definition

Prader-Willi syndrome (PWS) is a genetic condition caused by the absence of chromosomal material from chromosome 15. The genetic basis of PWS is complex. Characteristics of the syndrome include developmental delay, poor muscle tone, short stature, small hands and feet, incomplete sexual development, and unique facial features. Insatiable appetite is a classic feature of PWS. This uncontrollable appetite can lead to health problems and behavior disturbances.

Description

The first patients with features of PWS were described by Drs. Prader, Willi, and Lambert in 1956. Since that time, the complex genetic basis of PWS has begun to be understood. Initially, scientists found that individuals with PWS have a portion of genetic material deleted (erased) from chromosome 15. In order to have PWS, the genetic material must be deleted from the chromosome 15 received from one's father. If the deletion is on the chromosome 15 inherited from one's mother, a different syndrome develops. This was an important discovery. It demonstrated for the first time that the genes inherited from one's mother can be expressed differently than the genes inherited from one's father.

Over time, scientists realized that some individuals with PWS do not have a deletion of genetic material from chromosome 15. Further studies found that these patients inherit both copies of chromosome 15 from their mother. This is not typical. Normally, an individual should receive one chromosome 15 from one's father and one chromosome 15 from one's mother. When a person receives both **chromosomes** from the same parent it is called "uniparental disomy." When a person receives both chromosomes from one's mother it is called "maternal uniparental disomy."

Scientists are still discovering other causes of PWS. A small number of patients with PWS have a change (mutation) in the genetic material on the chromosome 15 inherited from their father. This mutation prevents certain genes on chromosome 15 from working properly. PWS develops when these genes do not work normally.

Newborns with PWS generally have poor muscle tone (hypotonia) and do not feed well. This can lead to poor weight gain and failure to thrive. Genitalia can be smaller than normal. Hands and feet are also typically smaller than normal. Some patients with PWS have unique facial characteristics. These unique facial features are typically subtle and only detectable by physicians.

As children with PWS age, development is typically slower than normal. Developmental milestones, such as crawling, walking, and talking occur later than usual. Developmental delay continues into adulthood for approximately 50% of individuals with PWS. At about one to two years of age, children with PWS develop an uncontrollable, insatiable appetite. Left to their own devices, individuals with PWS will eat until they have life-threatening obesity. The desire to eat can lead to significant behavior problems.

The symptoms and features of PWS require life-long support and care. If food intake is strictly monitored and various therapies provided, individuals with PWS have a normal life expectancy.

Genetic profile

In order to comprehend the various causes of PWS, the nature of chromosomes and genes must be well-understood. Human beings have 46 chromosomes in the cells of their body. Chromosomes contain genes. Genes regulate the function and development of the body. An individual's chromosomes are inherited from their parents. A child should receive 23 chromosomes from the mother and 23 chromosomes from the father.

The 46 chromosomes in the human body are divided into pairs. Each pair is assigned a number or a letter. Chromosomes are divided into pairs based on their physical characteristics. Chromosomes can only be seen when viewed under a microscope. Chromosomes within the

same pair appear identical because they contain the same genes.

Most chromosomes have a constriction near the center called the centromere. The centromere separates the chromosome into long and short arms. The short arm of a chromosome is called the "p arm." The long arm of a chromosome is called the "q arm."

Chromosomes in the same pair contain the same genes. However, some genes work differently depending on if they were inherited from the egg or the sperm. Sometimes, genes are silenced when inherited from the mother. Other times, genes are silenced when inherited from the father. When genes in a certain region on a chromosome are silenced, they are said to be "imprinted." Imprinting is a normal process. Imprinting does not typically cause disease. If normal imprinting is disrupted a genetic disease can develop.

Individuals should have two complete copies of chromosome 15. One chromosome 15 should be inherited from the mother, or be "maternal" in origin. The other chromosome 15 should be inherited from the father, or be "paternal" in origin.

Several genes found on the q arm of chromosome 15 are imprinted. A **gene** called "SNPRN" is an example of one of these genes. It is normally imprinted, or silenced, if inherited from the mother. The imprinting of this group of maternal genes does not typically cause disease. The genes in this region should not be imprinted if paternal in origin. Normal development depends on these paternal genes being present and active. If these genes are deleted, not inherited, or incorrectly imprinted, PWS develops.

Seventy percent of the cases of PWS are caused when a piece of material is deleted, or erased, from the paternal chromosome 15. This deletion happens in a specific region on the q arm of chromosome 15. The piece of chromosomal material that is deleted contains genes that must be present for normal development. These paternal genes must be working normally, because the same genes on the chromosome 15 inherited from the mother are imprinted. When these paternal genes are missing, the brain and other parts of the body do not develop as expected. This is what causes the symptoms associated with PWS.

In 99% of the cases of PWS the deletion is sporadic. This means that it happens randomly and there is not an apparent cause. It does not run in the family. If a child has PWS due to a sporadic deletion in the paternal chromosome 15, the chance the parents could have another child with PWS is less than 1%. In less than 1% of the cases of PWS there is a chromosomal rearrangement in the family which causes the deletion. This chromosomal rearrangement is called a "translocation." If a parent has a translocation the risk of having a child with PWS is higher than 1%.

PWS can also develop if a child receives both chromosome 15s from his or her mother. This is seen in approximately 25% of the cases of PWS. Maternal uniparental disomy for chromosome 15 leads to PWS because the genes on the chromosome 15 that should have been inherited from the father are missing. These paternal genes must be present, since the same genes on both the chromosome 15s inherited from the mother are imprinted.

PWS caused by maternal uniparental disomy is sporadic. This means that it happens randomly and there is no apparent cause. If a child has PWS due to maternal uniparental disomy the chance the parents could have another child with PWS is less than 1%.

Approximately 3–4% of patients with PWS have a change (mutation) in a gene located on the q arm of chromosome 15. This mutation leads to incorrect imprinting and causes genes inherited from the father to be imprinted or silenced. These genes should not normally be imprinted. If a child has PWS due to a mutation that changes imprinting, the chance the parents could have another child with PWS is approximately 5%.

It should be noted that if an individual has a deletion of the same material from the q arm of the maternal chromosome 15 a different syndrome develops. This syndrome is called **Angelman syndrome**. Angelman syndrome can also happen if an individual receives both chromosome 15s from the father.

Demographics

PWS affects approximately one in 10,000 to 25,000 live births. It is the most common genetic cause of life-threatening obesity. It affects both males and females. PWS can be seen in all races and ethnic groups.

Signs and symptoms

Infants with PWS have weak muscle tone (hypotonia). This hypotonia causes problems with sucking and eating. Infants with PWS may have problems gaining weight. Some infants with PWS are diagnosed with "failure to thrive" due to slow growth and development. During infancy, babies with PWS may also sleep more than normal and have problems controlling their temperature.

Some of the unique physical features associated with PWS can be seen during infancy. Genitalia that is smaller

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Centromere—The centromere is the constricted region of a chromosome. It performs certain functions during cell division.

Deletion—The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

FISH (fluorescence *in situ* hybridization)—Technique used to detect small deletions or rearrangements in chromosomes by attempting to attach a fluorescent (glowing) piece of a chromosome to a sample of cells obtained from a patient.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hyperphagia—Over-eating.

Hypotonia—Reduced or diminished muscle tone.

Imprinting—Process that silences a gene or group of genes. The genes are silenced depending on if they are inherited through the egg or the sperm.

Maternal—Relating to the mother.

Maternal uniparental disomy—Chromosome abnormality in which both chromosomes in a pair are inherited from one's mother.

Methylation testing—DNA testing that detects if a gene is active, or if it is imprinted.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Paternal—Relating to one's father.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Uniparental disomy—Chromosome abnormality in which both chromosomes in a pair are inherited from the same parent.

than normal is common. This may be more evident in males with PWS. Hands and feet may also be smaller than average. The unique facial features seen in some patients with PWS may be difficult to detect in infancy. These facial features are very mild and do not cause physical problems.

As early as six months, but more commonly between one and two years of age, a compulsive desire to eat develops. This uncontrollable appetite is a classic feature of PWS. Individuals with PWS lack the ability to feel full or satiated. This uncontrollable desire to eat is thought to be related to a difference in the brain, which controls hunger. Over-eating (hyperpahgia), a lack of a desire to exercise, and a slow metabolism places individuals with PWS at high risk for severe obesity. Some individuals with PWS may also have a reduced ability to vomit.

Behavior problems are a common feature of PWS. Some behavior problems develop from the desire to eat. Other reported problems include obsessive/compulsive behaviors, **depression**, and temper tantrums. Individuals with PWS may also pick their own skin (skin picking). This unusual behavior may be due to a reduced pain threshold.

Developmental delay, learning disabilities, and mental retardation are associated with PWS. Approximately 50% of individuals with PWS have developmental delay. The remaining 50% are described as having mild mental retardation. The mental retardation can occasionally be more severe. Infants and children with PWS are often delayed in development.

Puberty may occur early or late, but it is usually incomplete. In addition to the effects on sexual development and fertility, individuals do not undergo the normal adolescent growth spurt and may be short as adults. Muscles often remain underdeveloped and body fat increased.

Diagnosis

During infancy the diagnosis of PWS may be suspected if poor muscle tone, feeding problems, small genitalia, or the unique facial features are present. If an infant has these features, testing for PWS should be performed. This testing should also be offered to children and adults who display features commonly seen in PWS (developmental delay, uncontrollable appetite, small genitalia, etc.). There are several different genetic tests that can detect PWS. All of these tests can be performed from a blood sample.

Methylation testing detects 99% of the cases of PWS. Methylation testing can detect the absence of the paternal genes that should be normally active on chromosome 15. Although methylation testing can accurately diagnose PWS, it can not determine if the PWS is caused by a deletion, maternal uniparental disomy, or a mutation that disrupts imprinting. This information is important for **genetic counseling**. Therefore, additional testing should be performed.

Chromosome analysis can determine if the PWS is the result of a deletion in the q arm of chromosome 15. Chromosome analysis, also called karyotyping, involves staining the chromosomes and examining them under a microscope. In some cases the deletion of material from chromosome 15 can be easily seen. In other cases, further testing must be performed. FISH (fluorescence in-situ hybridization) is a special technique that detects small deletions that cause PWS.

More specialized DNA testing is required to detect maternal uniparental disomy or a mutation that disrupts imprinting. This DNA testing identifies unique DNA patterns in the mother and father. The unique DNA patterns are then compared with the DNA from the child with PWS.

PWS can be detected before birth if the mother undergoes **amniocentesis** testing or chorionic villus sampling (CVS). This testing would only be recommended if the mother or father is known to have a chromosome rearrangement or if they already have a child with PWS syndrome.

Treatment and management

There is currently no cure for PWS. Treatment during infancy includes therapies to improve muscle tone. Some infants with PWS also require special nipples and feeding techniques to improve weight gain.

Treatment and management during childhood, adolescence, and adulthood is typically focused on weight control. Strict control of food intake is vital to prevent severe obesity. In many cases, food must be made inaccessible. This may involve unconventional measures such as locking the refrigerator or kitchen cabinets. A lifelong restricted-calorie diet and regular exercise program are also suggested. Unfortunately, diet medications have not been shown to significantly prevent obesity in PWS. However, growth hormone therapy has been shown to improve the poor muscle tone and reduced height typically associated with PWS.

Special education may be helpful in treating developmental delays and behavior problems. Individuals with PWS typically excel in highly structured environments.

Prognosis

Life expectancy is normal and the prognosis good if weight gain is well controlled.

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ORGANIZATIONS

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557. Fax: (202) 966-8553. <http://www.geneticalliance.org>.

International Prader-Willi Syndrome Organization. Bizio 1, 36023 Costozza, Vicenza, Italy +39 0444 555557. Fax: +39 0444 555557. <http://www.ipwso.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Prader-Willi Foundation. 223 Main St., Port Washington, NY 11050. (800) 253-7993. <http://www.prader-willi.org>.

Prader-Willi Syndrome Association. 5700 Midnight Pass Rd., Suite 6, Sarasota, FL 34242-3000. (941) 312-0400 or (800) 926-4797. Fax: (941) 312-0142. <http://www.pwsausa.org PWSAUSA@aol.com>.

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GeneClinics. <http://www.geneclinics.org/profiles/pws/details.html>.

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Holly Ann Ishmael, MS, CGC

Prion diseases

Definition

Prion diseases are a class of degenerative central nervous system disorders. They are unique in that while a genetic component of the syndrome exists, prion diseases may also be transmitted, and the infectious agent of the disease is a protein. Dr. Stanley Prusiner coined the term "prion," meaning "proteinaceous infectious particle," in 1982. Dr. Prusiner's controversial, but finally accepted, research in the area of prion diseases led to his winning the Nobel Prize in Medicine in 1997.

Description

As of early 2001, there are five forms of prion disease known to occur in humans: kuru, Creutzfeldt-Jakob disease (CJD), Gertsmann-Straussler-Scheinker disease (GSS), fatal familial insomnia (FFI), and new variant Creutzfeld-Jakob disease, popularly known as "mad cow disease." The prion diseases are also called transmissible spongiform encephalopathies because they can be transmitted between unrelated individuals and they sometimes cause a sponge-like encephalopathy, or degeneration of the brain tissue, in which holes and other abnormal structures are formed in the brain. Prion diseases have also been identified in animals and include scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cows, feline spongiform encephalopathy in cats, and chronic wasting disease in mule, deer, and elk.

Prion diseases have all been associated with the function of a specific cellular protein named the prion protein (PrP). Like all cellular proteins, PrP is a long-chain molecule consisting of linked amino acids. A protein can assume many shapes: twisted into a spiral helix as in **DNA**, extended into linear strands, or folded into sheets of aligned strands. Different shapes of the same molecular sequence are called isomers. It is theorized that the normal form of cellular PrP is a compact shape consisting mainly of four helix regions, whereas in the abnormal isomer (the prion), the protein is refolded into a sheet-helix combination. Furthermore, this prion, through an unknown mechanism, triggers the conversion of normal PrP to the abnormal shape. The abnormal isomer acts as a template to change more and more normal PrP to the abnormal structure. Therefore, once the protein exists in the abnormal form, it is an infectious agent that can be transmitted from one person to another.

Normal proteins are processed by proteases, which are enzymes present in the body that act to break down excess proteins. However, the abnormal isomer of the prion protein is protease resistant and cannot be broken down by the body's protease enzymes. Therefore, the abnormal prion protein continues to be produced without being processed. This leads to an accumulation of the abnormal protein in the body. In several forms of prion disease, the abnormal prion protein aggregates in deposits, or plaques, in the brain tissue. It is believed that once the abnormal prion protein accumulates to a certain level in the body, the physical symptoms of impaired mental and physical functioning begin to show themselves. However, the exact mechanisms by which the abnormal isomer causes disease are not known. The onset of symptoms often does not occur until the patient is elderly, suggesting that either the rate of accumulation of the abnormal protein is initially slow, or that some triggering event late in life causes the initial formation of the abnormal isomer, after which the disease can spread.

The normal function of the prion protein is not completely understood, but it is known to be involved with the functions of the synapses (nerve connections) in the brain. PrP is found in the highest concentrations in the brain. PrP is also found in the eyes, lungs, heart, kidney, pancreas, testes, blood, and in the neuromuscular junction. The conversion of normal PrP to the infectious, abnormal isomer form may disrupt the normal functions of the prion protein, and this may be another cause of the degenerative symptoms of the disease.

Body tissues containing the abnormal isomer are a source of transmission of the disease between people and even across species. Prion diseases are also found in animals, and in animal studies it has been shown that the disease can be spread through the ingestion of infected brain tissue. The transmission can also cross the species barrier; it has been found that cows became affected by prion disease after eating feed contaminated with infected sheep brain tissue. It is widely speculated that the outbreak of mad cow disease, the most publicized prion disease, was caused by infection from affected cows in the United Kingdom, although the mode of transmission has still not been determined. Transmission through oral ingestion was also shown to be the cause of kuru in the Fore tribe of New Guinea. After the Fore abandoned their practice of ritual cannibalism in which they consumed the brain tissue of ancestors, the incidence of kuru all but disappeared. Other cases of human infection have been shown to be iatrogenic; in other words, transmitted inadvertently during medical treatment. Most of these iatrogenic cases involve direct contact with brain and nervous system tissue. For example, CJD has been reported to result from the use of contaminated surgical instruments, corneal implants, implantation of dura matter or electrodes in the brain, and from the injection of human

growth hormones derived from cadaverous pituitary glands.

Other modes of transmission have been shown to be less efficient in animal studies. The recent outbreak of new variant CJD caused increased concern about possible transmission through blood transfusions and plasma-derived products, but no case of new variant CJD has been proven to result from blood transfusion as of 2001. Laboratory and epidemiological evidence supporting a strong risk of the spread of prion disease through blood transfusion is not present, even though this area has been intensively studied.

Genetic profile

The **gene** that encodes the prion protein has been mapped to chromosome 20p12. This gene has been named the PRNP gene. Mutations in the PRNP gene can cause alterations in the chemical sequence of amino acids in the prion protein, and this change is believed to make the protein more susceptible to assuming the abnormal conformation. Over 20 different mutations of the gene have been identified, encompassing point mutations (one base pair substituted for another in the gene sequence), insertions (additions to the gene sequence), and deletions (missing parts of the gene sequence). Depending on the specific mutation, different types of prion disease can appear in the patient.

It is estimated that 10-15% of prion disease cases are caused by inherited mutations of the PRNP gene. Because of the delayed onset of the disease and the wide variation in symptoms, more exact statistics are difficult to determine. The **inheritance** pattern is autosomal dominant, meaning that if either parent passes the mutated gene to their offspring, the child will be affected by the disease. A parent with prion disease has a 50% probability of passing on the mutated gene to his or her child.

Another genetic factor important in prion disease is the genetic sequence of the PRNP gene. Like all genes, the PRNP gene is made up of two strands of DNA. Each DNA strand consists of a sequence of chemical structures called bases, and the two strands together form a sequence of base pairs. Three base pairs together form a unit called a codon, and each codon codes for a specific amino acid. At codon 129 of the PRNP gene, either the amino acid methionine (Met) or valine (Val) can be encoded. Since one gene is inherited from each parent, an individual may either be homozygous, having two of the same amino acids (Met-Met or Val-Val) at this position; or, heterozygous, having different amino acids (Met-Val). Individuals who are homozygous appear to be more susceptible to infection of prion diseases, because it has been shown that a greater percentage of those infected are homozygous than in the general population. Also, the clinical symptoms, or phenotype, of the prion disease can differ based on whether the individual is Met-Met or Val-Val homozygous, and whether the individual has Met or Val on the same gene as another mutation. For example, a specific point mutation at codon 178 has been found to cause familial CJD if the individual has Val at codon 129 on the mutated gene, while the same mutation causes FFI when the individual has Met at codon 129.

Demographics

Prion diseases occur worldwide with a rate of one to two cases per one million. CJD is the most common of the prion diseases, while GSS and FFI are extremely rare, and kuru is now virtually nonexistant due to the abandonment of the practice of cannibalism. There is no gender link to the disease. Several forms of prion disease usually do not cause identifiable symptoms until the individual is more than 60 years old, although other forms have an earlier onset and are seen in teenagers and young adults.

Since prion disease can be either inherited or transmitted through infection, the demographics of the disease have both familial and environmental patterns. Inherited CJD is found with high frequency in Libyan Jews and also in other descendants of Sephardic Jews in Greece, Tunisia, Israel, Italy, Spain, and perhaps South America. Other genetic clusters have been identified in Slovakia, Poland, France, and Germany. Fatal familial insomnia has been linked to family pedigrees in Italy, Australia, and the United States, among others. Families with GSS syndrome have been found in several countries in North America and Europe.

The environmental clusters of the disease include the Fore, a remote tribe of New Guinea in which kuru was transmitted through the practice of ritual cannibalism; a group of over 80 cases in Japan resulting from dura mater (brain membrane) grafts from a single surgical supply company; over 100 cases resulting from cadaveric human growth hormone injections in Europe and the United States; and, most famously, the 40-plus cases of new variant CJD or mad cow disease in the United Kingdom.

Signs and symptoms

Prion disease primarily affects the brain and central nervous system, so the symptoms associated with the disease are all related to neurological function. These may include loss of muscular coordination and uncontrollable body movements (ataxia), visual problems, hallucinations, behavioral changes, difficulty in thinking clearly or remembering, sleep disturbances, speech impairment, and insanity. General complaints such as headache,

diminished appetitie, and fatigue may occur prior to the onset of the more serious symptoms. The exact combination and severity of these symptoms varies widely between cases and types of prion disease.

CJD, the most common of the human prion diseases, is characterized by a rapid deterioration in mental function from confusion and memory loss into severe **dementia**, accompanied by loss of muscular control (ataxia) and twitching or spasmodic motion (myoclonus). Other symptoms include vision and speech impairment. A scan of electrical activity in the brain, called an electroencephalogram (EEG), will often show an abnormal periodic spike pattern. The onset of symptoms usually occurs when the patient is over age 50 and death follows within one to five years. Microsopic holes, or vacuoles, in the brain tissue, which give it a "spongiform" appearance, are characteristic of CJD.

Gertsmann-Straussler-Scheinker syndrome (GSS) encompasses a variety of disorders. One form of the disease (the ataxic form) is first characterized by an unsteady walk sometimes accompanied by leg pains. These motor problems get worse over several years and are finally accompanied by mental and behavioral breakdown. By contrast, dementia is the main characteristic of the telencephalic form of GSS, accompanied by rigidity, the inability to make facial expressions, tremors, and stuttering or stammering. In another form of the disease, GSS with neurofibrillary tangles, the main features are loss of muscle coordination (ataxia), tremors, and progressive insanity. As in CJD, the affected individuals are usually in their fifties or older, and the progression of the disease may take from two to six years.

The most noticeable sign of fatal familial insomnia (FFI) is the untreatable and progressively worse difficulty in sleeping. The affected individual then begins to experience complex hallucinations which are often enacted dreams. Excessive sweating, irregular heartbeat, high blood pressure, and hyperventilation are other symptoms. Motor impairment may be present. Shortened attention span and memory loss has been observed. In the terminal stages, stupor and coma precede death. The average age at onset of symptoms is the mid-forties, and the disease progresses rapidly with death resulting after about one year. Autopsy reveals the formation of dense tangles of neural fibers and astrocytes in the thalamus region of the brain.

Kuru was called the "shivering" disease by the Fore tribe members because its primary symptom was twitching and shaking of the body. This twitching began slowly and was not present when the person was completely still, but then progressively worsened until any attempt at motion led to drastic and uncontrollable body movements, and the individual could no longer stand or walk. Mental insanity usually did not appear until the terminal stages of the disease. The onset of symptoms usually occurred in middle-aged individuals and the course of the disease was short: three to 12 months.

KEY TERMS

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Iatrogenic—Caused by (-genic) doctor (iatro-). An iatrogenic condition is a condition that is caused by the diagnosis or treatment administered by medical professionals. Iatrogenic conditions may be caused by any number of things, including: unsterile medical instruments or devices, contaminated blood or implantations, or contaminated air within the medical facility.

Isomers—Two chemicals identical in chemical composition (contain the same atoms in the same amounts) that have differing structures. The normal prion protein and the infectious prion protein are conformational isomers of one another. They have the same chemical structures, but for some reason, assume different shapes.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Prion—A term coined to mean "proteinaceous infectious particle." Prior to the 1982 discovery of prions, it was not believed that proteins could serve as infectious agents.

Protease—An enzyme that acts as a catalyst in the breakdown of peptide bonds.

Spongiform encephalopathy—A form of brain disease characterized by a "spongelike" appearance of the brain either on autopsy or via magnetic resonance imaging (MRI).

The early signs of new variant CJD are most often psychiatric disturbances. Abnormal sensations of prickling or itching (paresthesia) or pain even from light touches (dysesthesia) are often present. So far, individuals affected with new variant CJD are much younger in age, typically teenagers and young adults. The duration of the disease is one to two years. As in CJD, vacuoles are present in the brain, but they are associated with dense deposits, or plaques, of the abnormal PrP isomer.

Diagnosis

Because of the many different forms of the disease and the overlap in symptoms with other common syn-

dromes such as **Alzheimer disease**, prion diseases are often difficult to diagnosis. A diagnosis of prion disease should be considered in any adult patient with signs of neurological impairment such as uncontrollable body movements, confusion, loss of memory, and cognitive degeneration, or psychiatric abnormality. Periodic discharges of brain waves, as observed on an electroencephalogram (EEG), are present in many, but not all, cases of prion disease. A magnetic resonance imaging (MRI) scan of the brain can rule out other causes of brain disease and potentially identify some abnormalities associated with prion disease. A biopsy, or sampling, of brain tissue can reveal the presence of abnormal PrP, although this procedure is generally not used in elderly patients. **Genetic testing** can reveal those cases of prion disease that are caused by mutations. Bismuth, mercury, or lithium poisoning result in symptoms that are quite similar to prion disease. These poisonings can be differentially diagnosed by blood tests.

The diagnosis of prion disease can be definitively confirmed by the transmission of the disease to an animal host such as a genetically engineered mouse. However, the transmission period may be quite long, as much as six to seven months. After death, prion disease can also be validated by autopsy of the brain tissue.

Patients eventually identified with prion disease have been initially diagnosed with many other diseases including Alzheimer disease, **Huntington disease**, **Parkinson disease**, **schizophrenia**, multiple sclerosis, and myoclonic **epilepsy**. This illustrates the difficulty in identifying the disease and the importance of careful diagnosis to avoid unnecessary treatments.

Treatment and management

At present, there is no known treatment that can prevent or reverse the transformation of the prion protein into its aberrant form. All treatments for prion disease are directed towards management of the symptoms. These treatments may include psychoactive drugs, electroconvulsive therapy (ECT), and professional care to ensure that the loss of physical and mental functions do not lead to accidental injury or death. Research into more advanced treatments is focusing on the application of gene therapies to block the formation of infectious PrP and drugs, which could act to stabilize the normal PrP structure. As with any inherited disease, **genetic counseling** is important in the management of the familial forms of prion disease.

Prognosis

Since the forms of prion diseases vary widely, the age at onset and rate of worsening of symptoms are also quite variable, but all prion diseases are incurable and fatal with a duration anywhere from a few months to several years after onset.

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Paul A. Johnson

Progeria syndrome

Definition

Progeria syndrome is an extremely rare genetic disorder of unknown origin that manifests as premature aging in children. Progeria affects many parts of the body including the skin, bones, and arteries.

Description

Dr. Jonathan Hutchinson in 1886 and Dr. Hastings Gilford in 1904 first described this syndrome. The word progeria is coined from the Greek word *geras*, which means old age. Progeria syndrome is also known as Hutchinson-Gilford progeria syndrome, HGPS or Gilford syndrome.

Most patients appear normal at birth. Signs and symptoms usually begin to develop within the first one to two years of life. Changes in skin and failure to thrive (failure to gain weight) are usually evident first, the exception being four reported cases of possible neonatal progeria. All four infants died before twenty months of

age. Death in these cases appears to be related to intrauterine growth retardation and presentation of progeria signs and symptoms at birth. The neonatal cases did not exhibit the development of arteriosclerosis (hardening of the arteries). Arteriosclerosis is the most serious complication of progeria. Complications secondary to arteriosclerosis in childhood, adolescence, or adulthood are the leading cause of death.

Patients with progeria syndrome develop many other signs and symptoms which present a classical appearance. The majority of patients with progeria resemble each other. Common external findings include aging at an accelerated rate, alopecia (hair loss), prominent scalp veins, absence of fat under the skin (subcutaneous fat), **scleroderma** (thickening of the skin), a pinched nose, small face and jaw (micrognathia) relative to head size (bird face), delayed tooth formation, high pitched voice, and impaired or absence of sexual development. Patients are also known to experience stiffening of various joints, bone structure abnormalities, and the development of arteriosclerosis. Patients with progeria syndrome experience average intelligence and their cognitive abilities are usually not affected.

Genetic profile

Evidence suggests that the **gene** for progeria may be located on chromosome 1. Progeria is believed to be passed on in an autosomal dominant new mutation fashion. The disorder is transmitted to children by autosomal dominant **inheritance**. This means that either affected parent (father or mother) has a 50% chance of having a child (regardless of gender) with the disorder. New mutation refers to the chance change in the structure of a gene resulting in alterations in its function. This new mutation is believed to happen at conception sporadically and permanently (since neither parent is affected). New mutations occur as a result of both genetic and environmental factors. New mutations can be either chromosomal abnormalities or point mutations (specific alterations in the building blocks of genes called nucleotides). Research is ongoing to identify a more specific genetic mutation that causes progeria syndrome.

Demographics

Occurrence of progeria is sporadic and rare, though studies suggest frequency may be related to increased parental age and increased average difference in age of parents. Approximately 100 cases have been reported to date in the world with the reported incidence (number of absolute occurrence) being one in eight million.

KEY TERMS

Arteriosclerosis—Hardening of the arteries that often results in decreased ability of blood to flow smoothly.

Failure to thrive—Significantly reduced or delayed physical growth.

Progeria—Genetic abnormality that presents initially as premature aging and failure to thrive in children.

Scleroderma—A relatively rare autoimmune disease affecting blood vessels and connective tissue that makes skin appear thickened.

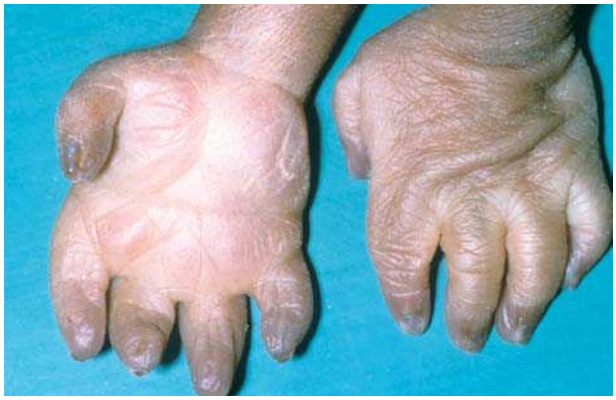
Signs and symptoms

Progeria syndrome is progressive. Signs develop over time.

- General—Patients are short and weigh less than is appropriate for height. Patients usually do not grow taller than 3.7 ft (1.15 m) or weigh over 40 lb (15 kg). Patients with progeria do not usually exhibit mental impairment.
- Skin—Skin is usually thin, dry, and wrinkled. The skin in the hands and feet is pushed inwards. The skin also exhibits color (pigmentation) changes, which presents clinically as yellow-brownish spots. Patients also have a decrease in fat below the skin (subcutaneous) except in the area below the navel. The nails of patients with progeria are small, thin, and poorly developed. Patients experience alopecia (hair loss) of the scalp, eyelashes, and eyebrows. Scalp veins become visible and prominent as hair loss progresses.
- Bones—There are several abnormalities in the skeletal structure. Refer to complete description under diagnosis heading.
- Eyes—Patients often appear to have prominent eyes. This is in part secondary to the alterations in bone structure of the face. Patients also may experience farsightedness (hyperopia) and astigmatism. Astigmatism refers to changes in the structure of the lens and cornea (parts of the internal structure of the eyes), which alter the eyes' ability to focus incoming visual images.

Diagnosis

Diagnosis is based upon physical appearance. Diagnosis is usually made within the first two years of life when patients develop skin changes and fail to grow.



Signs of premature aging in the hands of a patient diagnosed with progeria. *(Custom Medical Stock Photo, Inc.)*

Patients with progeria eventually develop skeletal system (bone and joint) changes. Patients show characteristic radiographic (x ray) findings. In general the skeleton is hypoplastic (underdeveloped). Patients have persistent anterior fontanelles (soft spots of skull in newborn children). Patients with progeria may also develop deterioration of the collarbone and end of the fingers. Hip joints are affected because of alteration in the bone structure of the femur (the bone which extends from the knee upwards to the pelvis). This causes the femur to sit in more of a straight-line relationship to the hip joint. This is abnormal and causes a wide-based gait (walking) and the appearance of a horse-riding stance. It is described as *coxa valga*. Some patients also show an increase in the amount of hyaluronic acid secreted in the urine. Hyaluronic acid is a substance in the body that is found in tissues such as cartilage. Cartilage is a flexible connective tissue that works as a joint stabilizer.

Treatment and management

There is no cure for progeria. Treatment is symptomatic and aimed at providing psychological support. Palliative measures such as wearing a wig may be beneficial. Relief from chest pain due to changes in arteries can be accomplished by nitroglycerin. Nitroglycerin is a medication that relaxes muscle fibers in blood vessels causing them to expand or dilate. This permits proper blood flow to affected areas, which enables cells and tissues to receive adequate amounts of the oxygen necessary for cell maintenance.

Experimental research management

Recent evidence suggested the benefit of giving nutritional therapy and growth hormone supplementation. The combination treatment of nutritional therapy and growth hormone supplementation demonstrated an increase in growth of Progeria patients, an increase in growth factors (chemicals which promote formation) within the blood, and a decrease in the patient's basal metabolic rate. Basal metabolic rate is the minimum amount of energy (calories) that an individual needs to ingest on a daily basis in order to execute normal activities and tasks.

Arteriosclerosis is most prominent in coronary (heart) arteries and the aorta (the largest artery in the body, which has many branches supplying oxygen filled blood to cells and tissues). Research indicates successful outcome from aggressive treatment of arteriosclerosis utilizing techniques such as coronary artery bypass (reconstruction of the heart arteries) or coronary artery balloon dilation (stretching the heart arteries in an attempt to allow increased blood flow).

Prognosis

Age of death ranges from seven to 27 years. One documented case reports an individual living to be 45 years of age. Death is usually secondary to arteriosclerosis complications such as heart failure, myocardial infarction (heart attack), or coronary thrombosis (when a clot from the heart moves to another location cutting the flow of blood to the new location).

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Children Living with Inherited Metabolic Diseases. The Quadrangle, Crewe Hall, Weston Rd., Crewe, Cheshire, CW1-6UR. UK 127 025 0221. Fax: 0870-7700-327. <http://www.climb.org.uk>.

International Progeria Registry. IBR Dept. of Human Genetics, 1050 Forest Hill Rd., Staten Island, NY 10314. (718) 494-5333. wtbibr@aol.com.

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Laith Farid Gulli, MD
Nicole Mallory, MS

Progressive tapetochoroidal dystrophy *see* **Choroideremia**

Propionic acidemia

Definition

Propionic acidemia is an inborn error of metabolism: a rare inherited disorder in which the body is unable to break down and use certain proteins properly. As a result, massive amounts of organic compounds (such as propionic acid, ketones, and fatty acids) build up in the blood and urine, interfering with normal body functions and development.

Description

Propionic acidemia, first described in 1961, usually shows up in the first few weeks after birth and, if untreated, results in mental and physical impairment. The disorder can have a broad range of clinical outcomes, ranging from the severe form that is fatal to newborns to the mild, late-onset form associated with periodic attacks of ketoacidosis, when organic compounds build up in the blood and urine. Other names for the disorder include ketotic hyperglycinemia, hyperglycinemia with ketoacidosis and lactic acidosis (propionic type), and propionyl CoA carboxylase (PCC) deficiency, types I and II.

Propionic acidemia can occur in isolation, or it can be a feature of multiple carboxylase deficiency, a condition involving abnormal production of many enzymes—all of which need biotin (a form of vitamin B)—as the result of an abnormality in biotin metabolism. Propionic acidemia is characterized by deficiency of an enzyme, propionyl CoA carboxylase, which the body requires to break down the amino acids isoleucine, valine, threonine, and methionine (chemical building blocks of proteins). The deficiency can be caused by abnormal genes for making propionyl CoA carboxylase (isolated propionic acidemia) or by abnormal genes for metabolizing biotin (propionic acidemia resulting from multiple carboxylase deficiency).

Genetic profile

Propionic acidemia is an autosomal recessive disorder; that is, if a man and woman each carry one abnormal **gene**, then 25% of their children are expected to be born with the disorder. Two genes, *PCCA* and *PCCB*, code for the two parts (alpha and beta subunits) of the propionyl CoA carboxylase molecule.

The PCCA gene controls the production of alpha subunit and is on chromosome 13. Alterations in the PCCA gene result in Type I propionic acidemia.

Researchers have identified 19 disease-causing mutations in the PCCA gene. Eight of these mutations result in an incomplete alpha subunit. Six mutations prevent the alpha subunit from binding biotin, which is required for propionyl CoA carboxylase to work properly, and results in multiple carboxylase deficiency. People who inherit two abnormal PCCA genes (homozygotes) produce only 1–5% of the normal amount of propionyl CoA carboxylase. People who inherit one normal and one abnormal PCCA gene (heterozygotes) produce 50% of the normal amount of enzyme.

The PCCB gene, which controls the production of beta subunit, is on chromosome 3. Mutations in this gene are responsible for Type II propionic acidemia.

Twenty-eight disease-causing mutations have been found in the PCCB gene. In people of Caucasian, Spanish, and Latin American heritage, researchers have found the most frequent mutation in about 32% of those with propionic acidemia. In people of Japanese heritage, two other mutations are most prevalent, occurring in 25% and 31% of Japanese patients. Homozygotes for the PCCB gene produce propionyl CoA carboxylase in amounts similar to homozygotes for the PCCA gene, but heterozygotes for the PCCB gene produce nearly normal amounts of propionyl CoA carboxylase. This is probably because many more beta subunits (four to five times more) are produced than alpha subunits, so even with decreased PCCB gene activity, enough beta subunits are available to combine with alpha subunits to make a complete molecule of propionyl CoA carboxylase.

Demographics

The frequency with which propionic acidemia occurs throughout the world is unknown because it is a rare disorder. Its occurrence does not appear to be specific to any particular population group. Considered to be prevalent among Inuits in Greenland, propionic acidemia has also been identified in other populations, including Austrian, Spanish, Latin American, Saudi Arabian, Amish, and Japanese people. Males and females are equally likely to be affected.

Signs and symptoms

Newborns with propionic acidemia are typically small and pale with poorly developed muscles. Symptoms that usually appear in the first weeks of life include poor feeding, vomiting, listlessness (lethargy), and ketoacidosis. Less often, infants with the disorder

KEY TERMS

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are "essential amino acids" which the body cannot make and must therefore be obtained from food).

Biotin—A growth vitamin of the vitamin B complex found naturally in liver, egg yolks, and yeast.

Ketoacidosis—A condition that results when organic compounds (such as propionic acid, ketones, and fatty acids) build up in the blood and urine.

Multiple carboxylase deficiency—A type of propionic acidemia characterized by an inability to metabolize biotin.

Propionic acid—An organic compound that builds up in the body if the proper enzymes are not present.

Propionyl CoA carboxylase—An enzyme that breaks down the amino acids isoleucine, valine, threonine, and methionine.

experience loss of body fluids (dehydration), seizures, and enlarged livers.

In some patients, the disorder appears later in life. Signs include facial abnormalities, such as puffy cheeks and an exaggerated "Cupid's bow" upper lip. Patients with late-onset propionic acidemia may have acute inflammation of the brain (encephalopathy) or be developmentally delayed. These patients may have periodic attacks of ketoacidosis, usually brought on by eating too much protein, becoming constipated, or having frequent infections.

Patients with propionic acidemia as the result of having multiple carboxylase deficiency often have ketoacidosis and their urine may have a distinct "tom cat's urine" odor. These patients may also have skin rash and loss of hair (alopecia).

Diagnosis

Physicians have only a few tests available that allow them to differentiate propionic acidemia from other inborn errors of metabolism. Tests that are absolutely specific for the disorder involve the measurement of propionyl CoA carboxylase and chemicals related to the reactions it affects. These tests are fairly uncommon and do not have published normal values.

Prenatal diagnosis of propionic acidemia is possible using cells obtained by **amniocentesis**. The cells can be tested for decreased activity of propionyl CoA carboxylase, for their ability to bind propionic acid, or for their methylcitrate levels.

In a newborn child, propionyl CoA carboxylase activity can be measured in white blood cells (leukocytes) from cord blood (blood from the umbilical cord). The infant's blood and urine can be tested for increased levels of propionic acid. These levels are tested as well in older children and adults who are suspected of having the disorder.

Physicians can use genetic tests to analyze **DNA** and identify the specific gene, PCCA or PCCB, that is abnormal.

Treatment and management

The accepted treatment for propionic acidosis is a low-protein diet. Daily protein intake must be limited to 0.5–1.5 g/kg. Patients should eat frequent meals and avoid fasting, because fasting increases the body's need for propionyl CoA carboxylate.

A low-protein diet keeps the number of ketoacidosis attacks to a minimum; however, such a diet does not prevent attacks. Physicians treat attacks of ketoacidosis by removing all protein from the patient's diet and giving the patient sodium bicarbonate and glucose. If the attack is severe, proteins may be removed from the patient's stomach by peritoneal dialysis.

Some patients may respond to a single oral dose (100 mg/kg) of L-carnitine, an organic compound. Others may be helped by antibiotics, which reduce the number of bacteria that produce propionic acid in the stomach. These are experimental treatments and have not been tested for long-term effects.

Patients with multiple carboxylase deficiency may receive biotin supplements (10 mg daily), which provide immediate, long-lasting improvement. Biotin supplements are not effective, however, for patients with other types of propionic acidemia.

Prognosis

The future of patients with propionic acidemia depends on the severity of the disorder. Left untreated, propionic acidemia in infants results in coma and death. With early diagnosis and treatment, some children are intellectually normal, while others' lives may be complicated by mental retardation and abnormal physical development. Some with popionic acidemia may be identified only during family studies. For patients with late-onset propionic acidemia, the disease can be controlled to some

extent by diet, but many of these patients will also be mentally and physically delayed.

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Linnea E. Wahl, MS

Propionyl CoA carboxylase (PCC) deficiency *see* **Propionic acidemia**

Prostate cancer

Definition

The prostate, a gland found only in men, is part of the reproductive system. Prostate cancer is a disease in which the cells of the prostate become abnormal and start to grow uncontrollably, forming tumors. Tumors that can spread to other parts of the body are called malignant tumors or cancers. Tumors that are not capable of spreading are said to be benign.

Description

The prostate is a gland that produces the semen, the fluid that contains sperm. The prostate is about the size of a walnut and lies just beneath the urinary bladder. Usually prostate cancer is slow growing, but it can grow faster in some instances. As the prostate cancer grows, some of the cells break off and spread to other parts of the body through the lymphatic or the blood systems. This is known as metastasis. The most common sites of spreading are the lymph nodes and various bones in the spine and pelvic region.

The cause of prostate cancer is not clear; however, several risk factors are known. The average age at diagnosis of prostate cancer is around 72. In fact, 80% of prostate cancer cases occur in men over the age of 65. As men grow older, the likelihood of getting prostate cancer increases. Hence, age appears to be a risk factor for prostate cancer. Race may be another contributing factor. African-Americans have the highest rate of prostate cancer in the world, while the rate in Asians is one of the lowest. However, although the rate of prostate cancer in native Japanese is low, the rate in Japanese-Americans is closer to that of white American men. This suggests that environmental factors also play a role in prostate cancer.

There is some evidence to suggest that a diet high in fat increases the risk of prostate cancer. Studies also suggest that nutrients such as soy isoflavones, vitamin E, selenium, vitamin D and carotenoids (including lycopene, the red color agent in tomatoes and beets) may decrease prostate cancer risk. Vasectomy may be linked to increased prostate cancer rates as well. Workers in industries, such as welding, with exposure to the metal cadmium appear to have a higher than average risk of prostate cancer. Male sex hormone levels also may be linked to the rate of prostate cancer. In addition, some studies have linked increased prostate cancer risk to smoking.

Genetic profile

An estimated 5–10% of prostate cancer is due to a hereditary cause. Among men with early prostate cancer, a hereditary cause is likely in up to a third of cases before age 60, and almost half of men diagnosed at age 55 or less. Studies have found around a two- to three-fold increased rate of prostate cancer in close relatives of men with the disease. Hereditary prostate cancer is likely in a family if there are three cases of prostate cancer in close relatives or three affected generations (either mother's or father's side), or two relatives with prostate cancer before age 55.

KEY TERMS

Anti-androgen drugs—Drugs that block the activity of the male hormone.

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Benign prostatic hyperplasia (BPH)—A noncancerous condition of the prostate that causes growth of the prostate tissue, thus enlarging the prostate and blocking urination.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Estrogen—A female sex hormone.

Hormone therapy—Treatment of cancer by changing the hormonal environment, such as testosterone and estrogen.

Lymph node—A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Prostatectomy—The surgical removal of the prostate gland.

Radiation therapy—Treatment using high-energy radiation from x ray machines, cobalt, radium, or other sources.

Rectum—The end portion of the intestine that leads to the anus.

Semen—A whitish, opaque fluid released at ejaculation that contains sperm.

Seminal vesicles—The pouches above the prostate that store semen.

Testicles—Two egg-shaped glands that produce sperm and sex hormones.

Testosterone—Hormone produced in the testicles that is involved in male secondary sex characteristics.

Trans-rectal ultrasound—A procedure where a probe is placed in the rectum. High-frequency sound waves that cannot be heard by humans are sent out from the probe and reflected by the prostate. These sound waves produce a pattern of echoes that are then used by the computer to create sonograms or pictures of areas inside the body.

Studies suggest that hereditary prostate cancer is likely to be caused by several different genes instead of a single **gene**. A gene, *HPC1* (hereditary prostate cancer gene 1), located on the first chromosome pair at 1q24-25, was the first gene suggested to cause hereditary prostate cancer. At least four other genes have been reported, including one thought to increase the risk of both prostate and brain tumors. Other genes known to increase the risk of other cancers, such as **breast cancer**, may also be linked to increased prostate cancer risk. Common variations in certain genes also may increase susceptibility to prostate cancer including one gene linked to male sex hormones. Since no clear cause has been identified for the majority of hereditary prostate cancer, **genetic testing**, as of 2001, is typically done through research studies.

Demographics

Prostate cancer is the most common cancer among men in the United States, and is the second leading cause of cancer deaths. The American Cancer Society estimates that in 2001, 198,100 new cases of prostate cancer will be diagnosed, and it will cause 31,500 deaths. One in six men in the United States will be diagnosed with prostate cancer. Prostate cancer affects African-American men about twice as often as it does Caucasian men, and the mortality rate among African-Americans is also higher. African-Americans have the highest rate of prostate cancer in the world. The prostate cancer rate varies considerably around the world. The highest rates are in North America and Western Europe, whereas the rates are moderate in Africa and lowest in Asia. It is unclear what roles genetics, diet, economics, and health care access play in these rates.

Signs and symptoms

Frequently, prostate cancer has no symptoms, and the disease is diagnosed when the patient goes for a routine screening examination. However, occasionally, when the tumor is larger or the cancer has spread to the nearby tissues, the following symptoms may occur:

• weak or interrupted flow of the urine

- frequent urination (especially at night)
- difficulty starting urination
- inability to urinate
- pain or burning sensation when urinating
- blood in the urine
- persistent pain in lower back, hips, or thighs (bone pain)
- difficulty having or keeping an erection (impotence)

Diagnosis

Although prostate cancer may be very slow-growing, it can be quite aggressive, especially in younger men. When the disease is slow-growing, it may go undetected. Because it may take many years for the cancer to develop, many men with the disease are likely to die of other causes rather than from the cancer.

Prostate cancer is frequently curable when detected early. However, because the early stages of prostate cancer may not have any symptoms, it often remains undetected until the patient goes for a routine physical examination. Diagnosis of the disease is made using some or all of the following tests.

Digital rectal examination (DRE)

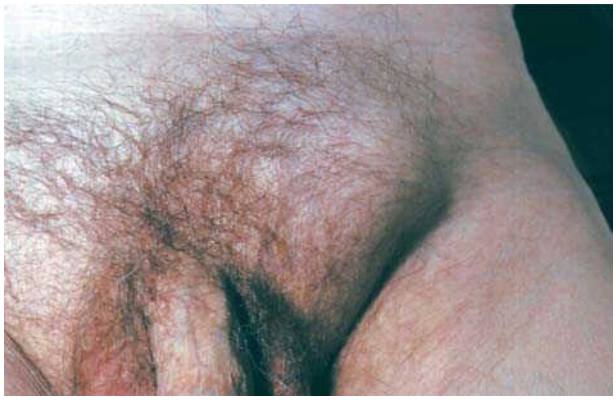
In order to perform this test, the doctor puts a gloved, lubricated finger (digit) into the rectum to feel for any lumps in the prostate. The rectum lies just behind the prostate gland, and a majority of prostate tumors begin in the posterior region of the prostate. If the doctor does detect an abnormality, he or she may order more tests in order to confirm these findings.

Blood tests

Blood tests are used to measure the amounts of certain protein markers, such as prostate-specific antigen (PSA), found circulating in the blood. The cells lining the prostate generally make this protein and a small amount can be detected in the bloodstream. However, prostate cancers typically produce a lot of this protein, and it can be easily detected in the blood. Hence, when PSA is found in the blood in higher than normal amounts (for the patient's age group), cancer may be present. Occasionally, other blood tests also are used to help with the diagnosis.

Transrectal ultrasound

A small probe is placed in the rectum and sound waves are released from the probe. These sound waves bounce off the prostate tissue and an image is created. Since normal prostate tissue and prostate tumors reflect the sound waves differently, the test can be used to detect tumors. Though the insertion of the probe into the rectum may be slightly uncomfortable, the procedure is generally painless and takes only about 20 minutes.



The enlarged lymph node in the groin area of this male patient is a sign of prostate cancer. *(Photo Researchers, Inc.)*

Prostate biopsy

If cancer is suspected from the results of any of the above tests, the doctor will remove a small piece of prostate tissue with a hollow needle. This sample is then checked under the microscope for the presence of cancerous cells. Prostate biopsy is the most definitive diagnostic tool for prostate cancer.

If cancer is detected during the microscopic examination of the prostate tissue, the pathologist will "grade" the tumor. This means that the tumor will be scored on a scale of 2-10 to indicate how aggressive the tumor is. Tumors with a lower score are less likely to grow and spread than are tumors with higher scores. This method of grading tumors is called the Gleason system. This is different from "staging" of the cancer. When a doctor stages a cancer, the doctor gives it a number that indicates whether it has spread and the extent of spread of the disease. In Stage I, the cancer is localized in the prostate in one area, while in the last stage, Stage IV, the cancer cells have spread to other parts of the body.

X rays and imaging techniques

X-ray studies may be ordered to determine whether the cancer has spread to other areas. Imaging techniques (such as computed tomography scans and magnetic resonance imaging), where a computer is used to generate a detailed picture of the prostate and areas nearby, may be done to get a clearer view of the internal organs. A bone scan may be used to check whether the cancer has spread to the bone.

The American Cancer Society and other organizations recommend that PSA blood testing and DRE be

offered to men with at least a 10-year life expectancy beginning at age 50. Men at higher risk for prostate cancer, such as those with a family history of the disease or African American men, may wish to consider screening at an earlier age such as 45. A low-fat diet may slow the progression of prostate cancer. Hence, the American Cancer Society recommends a diet rich in fruits, vegetables, and dietary fiber, and low in red meat and saturated fats, in order to reduce the risk of prostate cancer.

Treatment

The doctor and the patient will decide on the treatment after considering many factors. For example, the patient's age, the stage of the tumor, his general health, and the presence of any co-existing illnesses have to be considered. In addition, the patient's personal preferences and the risks and benefits of each treatment method are also taken into account before any decision is made.

Surgery

For early stage prostate cancer, surgery is frequently considered. Radical prostatectomy involves complete removal of the prostate. During the surgery, a sample of the lymph nodes near the prostate is removed to determine whether the cancer has spread beyond the prostate gland. Because the seminal vesicles (the gland where the sperm is made) are removed along with the prostate, infertility is a side effect of this type of surgery. In order to minimize the risk of impotence (inability to have an erection) and incontinence (inability to control urine flow), a procedure known as "nerve-sparing" prostatectomy is used.

In a different surgical method, known as the transurethral resection procedure or TURP, only the cancerous portion of the prostate is removed, by using a small wire loop that is introduced into the prostate through the urethra. This technique is most often used in men who cannot have a radical prostatectomy due to age or other illness, and it is rarely recommended.

Radiation therapy

Radiation therapy involves the use of high-energy x rays to kill cancer cells or to shrink tumors. It can be used instead of surgery for early stage cancer. The radiation can either be administered from a machine outside the body (external beam radiation), or small radioactive pellets can be implanted in the prostate gland in the area surrounding the tumor.

Hormone therapy

Hormone therapy is commonly used when the cancer is in an advanced stage and has spread to other parts of the body. Prostate cells need the male hormone testosterone to grow. Decreasing the levels of this hormone, or inhibiting its activity, may cause the cancer to shrink or stop growing. Hormone levels can be decreased in several ways. Orchiectomy is a surgical procedure that involves complete removal of the testicles, leading to a decrease in the levels of testosterone. Alternatively, drugs (such as LHRH agonists or anti-androgens) that bind to the male hormone testosterone and block its activity can be given. Another method tricks the body by administering the female hormone estrogen. When this is given, the body senses the presence of a sex hormone and stops making the male hormone testosterone. However, there are some side effects to hormone therapy. Men may have "hot flashes," enlargement and tenderness of the breasts, or impotence and loss of sexual desire, as well as blood clots, heart attacks, and strokes, depending on the dose of estrogen.

Chemotherapy

Chemotherapy is the use of drugs to kill cancer cells. The drugs can either be taken as a pill or injected into the body through a needle that is inserted into a blood vessel. This type of treatment is called systemic treatment because the drug enters the blood stream, travels through the whole body, and kills the cancer cells that are outside the prostate. Chemotherapy is sometimes used to treat prostate cancer that has recurred after other treatment. Research is ongoing to find more drugs that are effective for the treatment of prostate cancer.

Watchful waiting

Watchful waiting means no immediate treatment is recommended, but doctors keep the patient under careful observation. This option is generally used in older patients when the tumor is not very aggressive and the patients have other, more life-threatening illnesses. Prostate cancer in older men tends to be slow-growing. Therefore, the risk of the patient dying from prostate cancer, rather than from other causes, is relatively small.

Prognosis

According to the American Cancer Society, the survival rate for all stages of prostate cancer combined has increased from 50% to 87% over the last 30 years. Due to early detection and better screening methods, nearly 60% of the tumors are diagnosed while they are still confined to the prostate gland. The five-year survival rate for early

stage cancers is almost 99%. Sixty-three percent of the patients survive 10 years, and 51% survive 15 years after initial diagnosis. Studies on the prognosis of hereditary prostate cancer are ongoing.

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American Cancer Society. 1599 Clifton Rd. NE, Atlanta, GA 30329. (800) 227-2345. <http://www.cancer.org>.

American Foundation for Urologic Disease, Inc. 1128 North Charles St., Baltimore, MD 21201-5559. (410) 468-1808. <http://www.afud.org>.

National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda, MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

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Kristin Baker Niendorf, MS, CGC

Proteus syndrome

Definition

Proteus syndrome is characterized by excessive growth of cells. This can result in asymmetrical growth, benign (noncancerous) tumors, and pigmented skin lesions.

Description

Proteus syndrome is a rare condition. It was first described in 1979 by Michael Cohen. Hans-Rudolf Wiedemann named the condition after the Greek god Proteus, who could assume many forms. The disorder gained wide recognition when it became publicized that Joseph (John) Merrick, the person depicted in the movie *The Elephant Man*, probably had Proteus syndrome.

The excess growth of tissue that characterizes Proteus syndrome is progressive. It also tends to affect some tissues and not others. This can result in asymmetrical growth in the body, such as the skull, bones, spine, hands, feet, fingers, and toes. Proteus syndrome often results in overgrowth of one side of the body and not the other. Benign tumors on the surface of the skin or inside the body may also occur. Raised brown patches on the skin and an overgrowth of tissues on the soles of the feet or the palms of the hands are common. The types of tissues and organs that are affected and the severity of the effects vary from person to person and within the course of a lifetime. Proteus syndrome is sometimes associated with mental delay.

Genetic profile

The specific cause of Proteus syndrome is unclear. Proteus syndrome appears to occur randomly, suggesting that it is not inherited. Research suggests that Proteus syndrome results from an unknown **gene** that is changed (mutated) in some cells, but normal in other cells of the body. This is called mosaicism.

The tissues and organs that are affected in Proteus syndrome and the severity of effects probably depend on how many cells contain the mutated gene, and what type of cells contain it. Someone with many cells containing the changed Proteus gene are more likely to have more severe effects then someone with only a few cells changed. Someone with many cells changed in a particular part of the body, such as the hand, are more likely to have excessive growth in that area. The changed Proteus gene will affect cell growth even after the baby is fully developed, since cell division continues to take place and is necessary for the growth of tissues and organs and for the replacement of damaged cells. The changed Proteus gene mainly results in excessive growth of cells and tissues from infancy to adolescence.

Demographics

Only 100 to 200 cases of Proteus syndrome have been reported around the world. Both males and females are equally likely to be affected with Proteus syndrome.

Signs and symptoms

Individuals with Proteus syndrome can have a wide range of manifestations. The effects can also range from mild to severe. The most common manifestations of Proteus syndrome include:

• Overgrowth of hands, feet, fingers, or toes (gigantism)

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Benign tumor—An abnormal proliferation of cells that does not spread to other sites.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Mosaicism—A genetic condition resulting from a mutation, crossing over, or nondisjunction of chromosomes during cell division, causing a variation in the number of chromosomes in the cells.

Nevi—Plural of nevus.

Nevus—Any anomaly of the skin present at birth, including moles and various types of birthmarks.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Spleen—Organ located in the upper abdominal cavity that filters out old red blood cells and helps fight bacterial infections. Responsible for breaking down spherocytes at a rapid rate.

Spontaneous—Occurring by chance.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.

Tissue—Group of similar cells that work together to perform a particular function. The four basic types of tissue include muscle, nerve, epithelial, and connective tissues.

Vascular malformation—Abnormality of the blood vessels that often appears as a red or pink patch on the surface of the skin.

Vertebra—One of the 23 bones which comprise the spine. *Vertebrae* is the plural form.

- overgrowth of one side of the limbs, face, or body (hemihypertrophy)
- overgrowth of the connective tissue on the soles of the feet or palms of the hand or, less commonly, in the abdomen or nose (connective tissue nevi)
- darkened, discolored, and often rough and raised patches of skin (skin surface nevi)
- benign tumors on the skin surface and under the skin
- benign tumors of the fat cells (lipoma) or areas of significantly decreased or increased body fat
- abnormalities of the skull resulting in a large or asymmetrical head
- benign bony growths projecting outward from the end of the bones (exostosis)

People with Proteus syndrome can have curvature of the spine. They may also have an enlarged spleen or thymus. Approximately 12–13% of people with the disorder have cystic abnormalities of the lungs, which can interfere with the normal functioning of the lungs. Abnormalities in the blood vessels called vascular malformations, which appear as pink or red patches on the surface of the skin, are common. About one third of people with Proteus syndrome are mentally retarded; skull abnormalities are often seen in those with impairment. People with Proteus syndrome can have a distinctive facial appearance, with a long and narrow face, down-slanting eyes, wide and forward-tipping nostrils, a low nose bridge, and a mouth that remains open when at rest. Many effects can result from the presence of tumors and bony growths that affect other organs and tissues.

Sometimes mild or moderate effects of Proteus syndrome, such as benign tumors, are present at birth. As a person grows and develops, the tissue overgrowth pro-

gresses and changes. This progression is often irregular; it is characterized by periods of major overgrowth and other periods of absent overgrowth. The effects therefore change over the course of a lifetime. However, most changes occur before adolescence, since tissue overgrowth tends to plateau at that time.

Diagnosis

There is no blood test available to diagnose Proteus syndrome. A diagnosis can be made only by careful observation of the individual, perhaps over a period of time, and through imaging studies. These may include x ray evaluations of the skull and skeletal system; magnetic resonance imaging (MRI) of the limbs, nervous system, and abdomen; and computed tomography (CT) scans of the chest.

The great variability of Proteus syndrome from person to person makes it hard to diagnose. There are no definitive and universal diagnostic guidelines. Some tentative guidelines were established, however, at the First National Conference on Proteus Syndrome Diagnostic Criteria.

Treatment and management

There is no cure for Proteus syndrome. Treatment largely involves the management of effects of the disorder, such as the removal of tumors or bony overgrowths. Removal of tumors is not recommended, though, unless they are causing major problems, since these tumors usually grow back. Surgery to remove an overgrown portion of the bone should be performed only if the bony overgrowth is affecting normal functioning. Bony overgrowths in the ear, for example, may need to be removed if they are interfering with hearing. This type of surgery, however, can sometimes increase the growth of the remaining bone. Psychological counseling to help children with Proteus syndrome deal with the disorder should be considered. In order for counseling to be effective, it is preferable that it begins at a young age.

Prognosis

The long-term prognosis of Proteus syndrome is not known. The life expectancy is likely to vary greatly from person to person. Those with tumors and bony overgrowths affecting critical organs are likely to have a poorer prognosis.

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Proteus Syndrome Foundation. 6235 Whetstone Dr., Colorado Springs, CO 80918. (719)264-8445. abscit@aol.com. <http://www.kumc.edu/gec/support/proteus.html>.

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Lisa Maria Andres, MS, CGC

Prune-belly syndrome

Definition

Prune-belly syndrome is characterized by the following three findings: lack of abdominal muscles, undescended testes, and abnormal development of the urinary tract. Also known as Eagle-Barrett syndrome, this rare disorder was first described in 1839.

Description

Prune-belly syndrome displays a wide range of severity. Affected individuals will have little to no muscle in their abdominal wall. The abdomen will appear wrinkled, like a prune. In male infants, the testicles, although present, are usually not seen. They remain inside the infant’s abdomen. They fail to move to the normal position during development of the fetus. Undescended testes

KEY TERMS

Creatinine—A waste product of the body found in the urine. It is useful in determining the overall kidney function.

Pyelonephritis—Inflammation of the kidney commonly caused by bacterial infections.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

are a risk factor for infertility and testicular **cancer** later in the infant's life.

There are a variety of urinary tract abnormalities that occur in this syndrome. The kidneys may not form fully, and the level of development of the kidneys varies. The ureters, the tubes that connect the kidneys to the bladder, may be very large. In the portions that are very large, the urine may not be able to flow as well as normal. The bladder, the organ that holds the urine, may also be very large. A connection between the umbilicus and bladder may be present as well. The urethra may have areas that are very dilated and others that are very narrow. The narrowing may not allow the urine to flow out well. This blockage causes the bladder to become very large. The drainage of the fetus' bladder is what makes up the amniotic fluid during pregnancy. If the bladder cannot be drained, then not enough amniotic fluid will be present. The lack of amniotic fluid, or oligohydramnios, can cause poor formation of the fetus' lungs. The bladder in these patients may become so large that a mass can be seen and felt on the baby.

Ten percent of cases may have various abnormalities of the heart or large blood vessels. A percentage of cases will have abnormalities of their musculoskeletal system such as: dislocation of the hips, abnormal indentation of their chest, malformed feet or fingers, and a spine that is not aligned properly.

Genetic profile

A specific genetic defect is unknown. Multiple cases in families are rare but have been reported. The risk of recurrence in future pregnancies is unknown but is thought to be low.

Demographics

Despite the lack of a specific genetic defect or pattern of **inheritance**, over 95% of affected individuals are male. The incidence of this syndrome is estimated at one in 40,000 births.

Signs and symptoms

There are many symptoms that infants may experience in the newborn period. Most of these depend on the extent of damage that exists in the lungs and urinary tract. Infants who have poorly developed lungs, may be unable to breathe on their own at birth. They may also develop a collapsed lung or pneumothorax. If the infant does not have a normal rib cage then their ability to move air into and out of their lungs is impaired. This can lead to infections in the lung.

Since infants may not be able to eliminate of all their urine, they are at risk of having repeated urinary tract infections.

Diagnosis

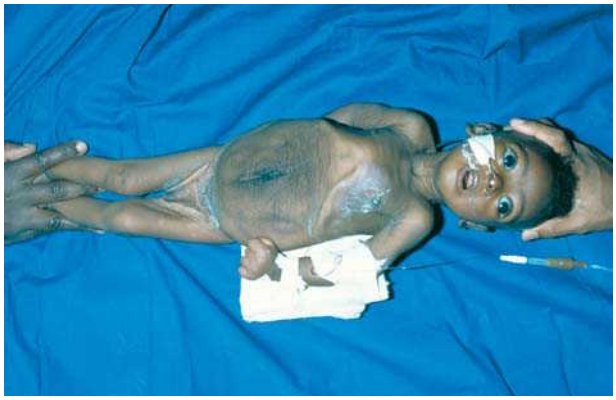
At birth, the syndrome is easily diagnosed based on the three findings that have been described. There is no specific prenatal or genetic test that can diagnose prune-belly syndrome. The diagnosis of prune-belly syndrome can be made in the prenatal period by ultrasound. Ultrasound can show some of the findings in this syndrome such as: distended bladder and ureters, oligohydramnios, and cryptorchidism. An enlarged bladder can be seen in other syndromes besides prune-belly, however, these findings on ultrasound should alert a physician to prune-belly as a possible cause.

Treatment and management

The potential treatments for prune-belly syndrome depend upon whether the diagnosis is made at birth or in utero. It also varies depending upon how severe the abnormalities are. Over the past two decades, different surgical procedures have been performed on fetuses in an attempt to correct the urinary tract obstructions that occur. One of these procedures is the vesicoamniotic shunt. This procedure relieves bladder obstructions by placing a tube in the fetal bladder allowing amniotic fluid to be produced as usual. The production of amniotic fluid allows for normal development of the lungs. There is not much information regarding the long-term outcomes for persons who receive these shunts. In infants who survive but have **renal failure**, kidney transplantation has been attempted with some success.

Prognosis

Approximately 20% of patients with this syndrome are stillborn. Thirty percent of infants do not survive past



The distinctive "prune-like" appearance of the abdominal area is evident in this infant. *(Custom Medical Stock Photo, Inc.)*

two years due to renal failure or infection. The remaining 50% of the infants will have a variety of urinary tract problems. A recent study looked at what factors may predict which children with prune-belly syndrome will develop renal failure. In this study, 35 patients with prune-belly syndrome between 1960 and 1997 were examined. Developing pyelonephritis (infection and inflammation of the kidney) at some point in time, having an elevated baseline creatinine, and having both kidneys look abnormal on an ultrasound were predictive for developing renal failure.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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David Elihu Greenberg, MD

Pseudo-Hurler disease *see* **GM1 gangliosidosis**

Pseudothalidomide syndrome *see* **Roberts SC phocomelia**

Pseudoxanthoma elasticum

Definition

Pseudoxanthoma elascticum (PXE) is an inherited connective tissue disorder in which the elastic fibers present in the skin, eyes, and cardiovascular system gradually become calcified and inelastic.

Description

PXE was first reported in 1881 by Rigal, but the problem with elastic fibers was described in 1986 by Darier who gave the condition its name. PXE is also known as Grönblad-Strandberg-Touraine syndrome and systemic elastorrhexis.

The course of PXE varies greatly between individuals. Typically, it is first noticed during adolescence as yellow-orange bumps on the side of the neck. Similar bumps may appear at other places where the skin bends a lot, like the backs of the knees and the insides of the elbows. The skin in these areas tends to get thick, leathery, inelastic, and acquire extra folds. These skin problems have no serious consequences, and for some people, the disease progresses no further.

Bruch's membrane, a layer of elastic fibers in front of the retina, becomes calcified in some people with PXE. Calcification causes cracks in Bruch's membrane, which can be seen through an ophthalmoscope as red, brown, or gray streaks called angioid streaks. The cracks can eventually (e.g., in 10–20 years) cause bleeding, and the usual resultant scarring leads to central vision deterioration. However, peripheral vision is unaffected.

Arterial walls and heart valves contain elastic fibers that can become calcified. This leads to a greater susceptibility to the conditions that are associated with hardening of the arteries in the normal aging population—high blood pressure, heart attack, stroke, and arterial obstruction—and, similarly, mitral valve prolapse. Heart disease and hypertension associated with PXE have been reported in children as young as four to 13 years of age. Although often appearing at a younger age, the overall incidence of these conditions is only slightly higher for people with PXE than it is in the general population.

KEY TERMS

Angioid streaks—Gray, orange, or red wavy branching lines in Bruch's membrane.

Bruch's membrane—A membrane in the eye between the choroid membrane and the retina.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Claudication—Pain in the lower legs after exercise caused by insufficient blood supply.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Deletion—The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

Dominant trait—A genetic trait where one copy of the gene is sufficient to yield an outward display of the trait; dominant genes mask the presence of recessive genes; dominant traits can be inherited from a single parent.

Elastic fiber—Fibrous, stretchable connective tissue made primarily from proteins, elastin, collagen, and fibrillin.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Mitral valve—The heart valve that prevents blood from flowing backwards from the left ventricle into the left atrium. Also known as bicuspid valve.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Recessive trait—An inherited trait or characteristic that is outwardly obvious only when two copies of the gene for that trait are present.

Arterial inelasticity can lead to bleeding from the gastrointestinal tract and, rarely, acute vomiting of blood.

Genetic profile

PXE is caused by changes in the genetic material, called mutations, that are inherited in either a dominant or recessive mode. A person with the recessive form of the disease (which is most common) must possess two copies of the PXE **gene** to be affected, and, therefore, must have received one from each parent. In the dominant form, one copy of the abnormal gene is sufficient to cause the disease. In some cases, a person with the dominant form inherits the abnormal gene from a parent with PXE. More commonly, the mutation arises as a spontaneous change in the genetic material of the affected person. These cases are called "sporadic" and do not affect parents or siblings, although each child of a person with sporadic PXE has a 50% risk to inherit the condition.

Both males and females can develop PXE, although the skin findings seem to be somewhat more common in females.

The actual genetic causes of this condition were not discovered until 2000. The recessive, dominant, and sporadic forms of PXE all appear to be caused by different mutations or deletions in a single gene called ABCC6 (also known as MRP6), located on chromosome 16. Although the responsible gene has been identified, how it causes PXE is still unknown.

Genetic researchers have since identified mutations in a number of persons with PXE, most of whom have been found to have the recessive type. Affected individuals in these families had mutations in both copies of the gene and parents, who are obligate carriers, had a mutation in only one copy. Contrary to the usual lack of symptoms in carriers of recessive genes, some carriers of recessive PXE have been found to have cardiovascular symptoms typical of PXE.

Although the recessive type is the most common, there are also familial and sporadic cases that have been found to be caused by dominant mutations in the ABCC6 gene.

Demographics

PXE is rare and occurs in about one in every 160,000 people in the general population. It is likely, though, that PXE is underdiagnosed because of the presence of mild symptoms in some affected persons and the lack of awareness of the condition among primary care physicians.

Signs and symptoms

A wide range in the type and severity of symptoms exists between people with PXE. The age of onset also varies, although most people notice initial symptoms during adolescence or early adulthood. Often, the first symptoms to appear are thickened skin with yellow bumps in localized areas such as the folds of the groin, arms, knees, and armpits. These changes can also occur in the mucous membranes, most often in the inner portion of the lower lip. The appearance of the skin in PXE has been likened to a plucked chicken or Moroccan leather.

Angioid streaks in front of the retina are present in most people with PXE and an ophthalmologic examination can be used as an initial screen for the condition. Persons with PXE often complain of sensitivity to light. Because of the progressive breakdown of Bruch's membrane, affected persons are at increased risk for bleeding and scarring of the retina, which can lead to decreased central vision but does not usually cause complete blindness.

Calcium deposits in the artery walls contribute to early-onset atherosclerosis, and another condition called claudication, inadequate blood flow that results in pain in the legs after exertion. Abnormal bleeding, caused by calcification of the inner layer of the arteries, can occur in the brain, retina, uterus, bladder, and joints but is most common in the gastrointestinal tract.

Diagnosis

The presence of calcium in elastic fibers, as revealed by microscopic examination of biopsied skin, unequivocally establishes the diagnosis of PXE.

Treatment and management

PXE cannot be cured, but plastic surgery can treat PXE skin lesions, and laser surgery is used to prevent or slow the progression of vision loss. Excessive blood loss due to bleeding into the gastrointestinal tract or other organ systems may be treated by transfusion. Mitral valve prolapse (protrusion of one or both cusps of the mitral heart valve back into the atrium during heart beating) can be corrected by surgery, if necessary.

Measures should be taken to prevent or lessen cardiovascular complications. People with PXE should control their cholesterol and blood pressure, and maintain normal weight. They should exercise for cardiovascular health and to prevent or reduce claudication later in life. They should also avoid the use of tobacco, thiazide antihypertensive drugs, blood thinners like coumadin, and non-steroidal anti-inflammatory drugs like aspirin and ibuprofen. In addition, they should avoid strain, heavy lifting, and contact sports, since these activities could trigger retinal and gastrointestinal bleeding.

People with PXE should have regular eye examinations by an ophthalmologist and report any eye problems immediately. Regular check-ups with a physician are also recommended, including periodic blood pressure readings.

Some people have advocated a calcium-restricted diet, but it is not yet known whether this aids the problems brought about by PXE. It is known, however, that calcium-restriction can lead to bone disorders.

Prognosis

The prognosis is for a normal life span with an increased chance of cardiovascular and circulatory problems, hypertension, gastrointestinal bleeding, and impaired vision. However, now that the gene for PXE has been identified, the groundwork for research to provide effective treatment has been laid. Studying the role of the ABCC6 protein in elastic fibers may lead to drugs that will improve or prevent the problems caused by PXE.

Genetic tests are now available that can provide knowledge needed to both diagnose PXE in symptomatic persons and predict it prior to the onset of symptoms in persons at risk. Prenatal diagnosis of PXE, by testing fetal cells for mutations in the ABCC6 gene, can be done in early pregnancy by procedures such as **amniocentesis** or chorionic villus sampling. For most people, PXE is compatible with a reasonably normal life, and prenatal diagnosis is not likely to be highly desired.

Genetic testing to predict whether an at-risk child will develop PXE may be helpful for medical management. A child who is found to carry a mutation can be monitored more closely for eye problems and bleeding, and can begin the appropriate lifestyle changes to prevent cardiovascular problems.

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PXE International, Inc. 23 Mountain Street, Sharon, MA 02067. (781) 784-3817. Fax: (781) 784-6672. PXEInter @aol.com. <http://www.pxe.org/>.

Barbara J. Pettersen, MS, CGC

Pyloric stenosis

Definition

Pyloric stenosis is a disorder that occurs when the pyloric sphincter muscle, which is found at the outlet of the stomach, thickens and becomes enlarged causing the cavity (lumen) of the pylorus to narrow and lengthen. This blocks the passage of food from the stomach to the small intestine (the portion of bowel that continues digestion after food leaves the stomach).

Description

Pyloric stenosis occurs due to enlargement of the walls of the pyloric sphincter. The pyloric sphincter is a circular smooth muscle at the outlet of the stomach that controls the flow of food from the stomach to the small intestine. The muscle cells become enlarged (hypertrophied) causing a narrowing (stenosis) of the pyloric lumen. This causes food to be pushed back into the stomach. Symptoms of pyloric stenosis typically appear two to six weeks after birth. In rare cases it occurs in older adults, not of genetic cause but due to an ulcer (inflammatory lesion of the mucous-like tissue in the stomach) or hardening of the tissue (fibrosis) at the outlet of the stomach. Alternate names associated with the disorder are Hypertrophic pyloric stenosis and Infantile hypertrophic pyloric stenosis.

Genetic profile

The exact cause of pyloric stenosis is unknown. It generally occurs in one in 300 births. The incidence of pyloric stenosis may be higher if a parent or sibling had the condition. It is also more common in the first-born child. Family correlation studies have shown that there is higher expression (concordance) of pyloric stenosis in identical twins (monozygotic) than in fraternal twins (dizygotic). The risk for first-degree relatives (brothers, sisters) of females is higher than those of males. This is also true of second-degree relatives (cousins).

KEY TERMS

Pyloric sphincter—Circular smooth muscle found at the outlet of the stomach.

Stenosis—The constricting or narrowing of an opening or passageway.

It has been suggested that motilin receptors, which are responsible for motility, might have an involvement in pyloric stenosis. The development of functional motilin receptors occurs around the age of onset for most cases of pyloric stenosis. Studies have found that the use of an antibiotic, called erythromycin for pertussis (a contagious respiratory disease also known as whooping cough) prophylaxis may increase the risk for pyloric stenosis. Erythromycin is a motilin agonist (acts on something to produce a predictable response) and high doses can cause an increase in non-propagated contractions and motility. The lack of neuronal nitric oxide synthase in pyloric tissue may cause a spasm (a twitching or involuntary contraction) in the pyloric muscle in individuals with pyloric stenosis. Neuronal nitric oxide synthase is needed for the synthesis of nitric oxide, which opposes the contraction force in active muscle.

Demographics

Pyloric stenosis affects males three to four times more than females and appears to have an increased incidence in caucasians.

Signs and symptoms

Symptoms include:

- Regurgitation and non-bilious vomiting. Infants may bring food back up during or after feeding. Vomiting may become projectile (expelled with force) and vomit may have a “coffee ground” color. Vomit should not contain stomach bile, which is acidic and a brownish-green color. This would be contraindicative of pyloric stenosis.
- Olive-sized abdominal mass. A mass about the size of an olive may be felt in the upper abdomen. The mass should be hard, mobile, and non-tender.
- Pylorospasm. A spasm of the pyloric muscle may occur due to increased motility.
- Additional abnormalities. These include hunger, irritability, lethargy (prolonged sleepiness or sluggishness), weight loss, decreased urine output, constipation, and gastric (stomach) peristalsis (rhythmic contraction of smooth muscle) from the left to right.

Diagnosis

An individual's medical history and physical assessment by a doctor are necessary for a diagnosis of pyloric stenosis. A palpable mass, the size of an olive, in the upper abdominal area usually confirms a diagnosis of pyloric stenosis. When physical findings are inconclusive, an abdominal ultrasound or barium study may be performed to confirm diagnosis. An ultrasound, the preferred method of confirmation, is a non-invasive study that uses high frequency sound waves to distinguish the image of internal structures of the body. A barium study involves the ingestion of a radiographic dye. The movement of the dye through the gastrointestinal (GI) tract can be followed by fluoroscopy or x ray studies. It has been suggested that the Lipper GI series may be an effective step in confirming pyloric stenosis. This test consists of aspirating (withdrawal of fluid) and measuring gastric contents. The amount of aspirated contents is indicative of pyloric stenosis and studies have demonstrated this method to be a reliable diagnostic tool.

In adults with symptoms of pyloric stenosis, a barium swallow study is used to diagnose the disorder. X rays are taken of the abdominal structures after the ingestion of the barium radioisotope (a radioactive form of a chemical element).

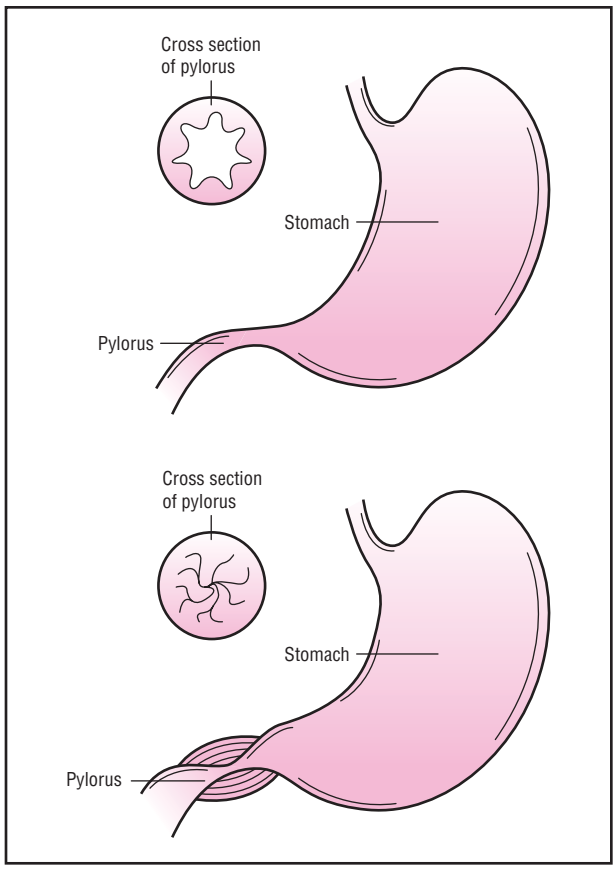
Treatment and management

As of 2000, the only treatment for pyloric stenosis is surgical pyloromyotomy. Making an incision into the pyloric muscle and spreading the walls of the muscle apart completes the surgery. This allows gastric mucosa to push up through the incision and relieve the blockage.

Blood analysis should be performed before surgery and intravenous (going into the vein) fluids should be given to correct electrolyte (sodium, potassium, calcium etc.) imbalances and rehydrate infants. Following surgery the infant should start on an oral electrolyte (elements necessary for cell functioning) solution (pedialyte). Feedings will be gradually increased until the infant is tolerating 2-3 ounces of breast-milk or formula without complications. The stomach needs time to heal; therefore vomiting due to increased feedings is common. Infants are usually discharged 24–48 hours following surgery. It has been suggested that rapid advancement of the strength and volume of feedings is effective and may allow for quicker discharge from the hospital.

Adults being treated for pyloric stenosis usually have a stomach tube inserted into the muscle that remains in place after sugery.

Recurrence of pyloric stenosis after surgery is rare. As of 2000, there has been no occurrence of conditions later in life related to the occurrence of pyloric stenosis during infancy.



These diagrams show the cross section of a normal pylorus in relation to a stomach with pyloris stenosis where the pylorus has become extremely narrowed. Constriction of the pyloris results from enlargement of the muscle surrounding it. *(Gale Group)*

Prognosis

The prognosis of pyloric stenosis is very good for those that are diagnosed early and treated with surgery. Life expectancy of infants diagnosed with pyloric stenosis is the same as that of the average individual. Parents should contact a doctor if pyloric stenosis is suspected.

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Laith Farid Gulli, MD
Tanya Bivins, BS

Pyruvate carboxylase deficiency

Definition

Pyruvate carboxylase deficiency (PCD) is a rare non-sex linked (autosomal) disorder that results from an insufficient amount of the enzyme pyruvate carboxylase. This disorder is inherited as a recessive trait and it is known to be caused by more than one different mutation in the same **gene** (allelic variants).

Description

There are two recognized types of pyruvate carboxylase deficiency, neonatal PCD (type B) and infantile onset PCD (type A). Neonatal PCD is associated with a complete, or near complete, inability to produce pyruvate carboxylase. Infantile onset PCD is associated with a chemical change in the pyruvate carboxylase enzyme that prevents this slightly different chemical from functioning as efficiently as the normal pyruvate carboxylase enzyme.

In order for the cells of the body to function properly, they must have energy. This energy comes in the form of the chemical ATP. ATP is primarily produced by breaking down carbohydrates and blood sugar (glucose) molecules. To begin the process of converting glucose and carbohydrates into usable energy, these molecules are first converted into pyruvate molecules. Once pyruvate molecules have been formed, one of two things will happen: if more energy is required by the cell, the molecules will be further broken down into ATP; or, if no additional energy is needed by the cell, the pyruvate molecules will be put back together to reform a glucose molecule.

These transformations of pyruvate are accomplished primarily by two enzymes: pyruvate dehydrogenase (PDH), an enzyme that begins the breakdown of the pyruvate into ATP, and pyruvate carboxylase, an enzyme that begins the chemical process to reform glucose molecules. The reformation of glucose from pyruvate is a vital step in cellular metabolism. It allows carbohydrate molecules to be converted into a more readily usable form (glucose). Glucose is not only easier to breakdown into the energy required by the cells, but it is also more able to be transported through the bloodstream than most other fuel sources. This is particularly important because certain cells (primarily those of the brain and nervous system) cannot breakdown larger molecules; they must get their energy directly from glucose.

Pyruvate carboxylase is, in effect, part of the "off switch" for the production of ATP from pyruvate. After a cell has received the amount of ATP it requires, it is the job of pyruvate carboxylase to re-convert the excess pyruvate molecules in that cell back into glucose molecules for storage or transport to another part of the body where they may be needed. Any molecules that are not put back together will degrade into lactic acid. This lactic acid will either be released into the bloodstream or it will buildup in the tissues. The buildup of lactic acid in the muscle tissues and red blood cells is normal during strenuous exercise. However, the accumulation of lactic acid in other tissues without exercise or without oxygen deprivation is symptomatic of an underlying problem in the normal metabolism of the cells.

People with PCD have either a complete inability or a severely limited ability to produce pyruvate carboxylase. Since these individuals cannot produce the amounts of this enzyme required to form glucose from pyruvate, this pyruvate is converted instead into lactic acid, which builds up in the cells. Additionally, since glucose cannot be adequately formed within the body of a pyruvate car-

boxylase deficient individual, all the glucose required by the body must be ingested. This causes a glucose shortage that leads to low blood sugar (hypoglycemia) and a progressive degeneration of the tissues, with the most profound effects observed in the brain and central nervous system, since these tissues are the most reliant on the use of glucose for energy.

Pyruvate carboxylase is also important in the process that removes excess nitrogen from the body (the urea cycle). Since pyruvate carboxylase deficient individuals do not have sufficient quantities of pyruvate carboxylase, they develop a build-up of nitrogen, in the form of ammonia, in the bloodstream and the tissues.

Genetic profile

The gene that is responsible for the production of pyruvate carboxylase has been localized to a small region of chromosome 11. There are at least three mutations in this gene that lead to type B PCD. There is only one known mutation that leads to type A PCD.

Both types of PCD are transmitted via a recessive trait which means that both parents must be carriers of the mutation in order for it to occur in their children. In the case of parents with one child affected with PCD, the likelihood that a second child will be affected with PCD is 25%.

Demographics

PCD is estimated to occur in approximately one in every 250,000 live births, although only 39 cases had been described in the literature prior to 2001.

Type A PCD is also called North American PCD because it occurs almost exclusively in Algonquin language-speaking Native North Americans. In the Micmac, Cree, and Ojibwa tribes of Canada, it is estimated that as high as one in 10 individuals are carriers of the mutation that causes type A PCD. This suggests a founder effect in these populations. A founder effect is a genetic term that means a single individual brought a mutation into a subpopulation at a time when the subpopulation was quite small. As a result, a large majority of the members of the subpopulation carry the mutation derived through direct ancestry to this one individual.

Type B PCD is also called French PCD because it has a much higher incidence among the French than among any other subpopulation.

Signs and symptoms

Type A, or infantile onset, PCD may be fatal prior to birth, or it may not present any symptoms until approximately three months of age. These individuals will show severe physical and mental delay. Additionally, children affected with type A PCD have a progressive degeneration of the entire brain and nervous system (necrotizing encephalomyelopathy) that eventually leads to death.

Type B, or neonatal, PCD is generally fatal prior to birth. In the rare instances of a liveborn child affected with type B PCD, severe growth delay (extremely low birth weight) and severe mental impairment are to be expected. Children born with type B PCD will fail to thrive and generally do not survive past the first three months of life.

Diagnosis

PCD is diagnosed primarily through blood tests to determine the blood concentrations of lactate and pyru-

KEY TERMS

Allelic variants—A disease is said to have allelic variants when different mutations in the same allele result in identical, or nearly identical, symptoms. An allele is the combined locations of a gene on the two paired chromosomes that contain this gene.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Biotin—A growth vitamin of the vitamin B complex found naturally in liver, egg yolks, and yeast.

Enzyme efficiency—The rate at which an enzyme can perform the chemical transformation that it is expected to accomplish. This is also called turnover rate. Individuals affected with type A PCD produce an enzyme that is much slower than the normal pyruvate carboxylase enzyme.

Necrotizing encephalomyelopathy—A progressive degeneration of the brain and central nervous system. This condition is fatal in nearly all individuals affected with type A pyruvate carboxylase deficiency.

Pyruvate carboxylase—The enzyme that is responsible for the first step in the conversion of pyruvate molecules into glucose molecules. Individuals with type A PCD produce a highly inefficient form of pyruvate carboxylase. Individuals with type B PCD either completely lack the ability to produce this enzyme, or they cannot produce it in sufficient quantities to sustain life.

vate. Extremely high levels of both of these chemicals in the blood indicate that a congenital problem in cellular metabolism is most likely present. PCD is often differentiated from other cellular metabolic disorders by the extreme speed with which glucose levels in the blood drop during fasting (fasting hypoglycemia) and the abnormally low levels of the chemical aspartic acid in the blood.

PCD can be tested prenatally by measuring the activity of pyruvate carboxylase in chorionic villi samples.

Treatment and management

Administration of aspartic acid has been successful in decreasing the pyruvate and lactate concentrations in the blood of some PCD affected individuals. But, this treatment does not repair the damage to the pyruvate carboxylase enzyme, so progressive degeneration of the nervous system is slowed only slightly and the outcome is still death.

Biotin (a B-complex vitamin) is a coenzyme to pyruvate carboxylase. It has been shown that type B PCD is responsive to treatment with biotin while type A is not. Therefore, in the rare instance of a liveborn child with type B PCD, life may be extended through the administration of biotin.

Prognosis

Without prenatal administration of enzyme replacement therapy (which is currently not available), in which the developing fetus is given an artificial form of pyruvate carboxylase, individuals affected with either type A or type B PCD will die either prior to birth or, generally, within the first six months of life. Without prenatal enzyme replacement therapy, most children affected with PCD are born with such brain and nervous system dysfunction that a decision has to be made about treatment to sustain life.

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Children Living with Inherited Metabolic Diseases. The Quadrangle, Crewe Hall, Weston Rd., Crewe, Cheshire, CW1-6UR. UK 127 025 0221. Fax: 0870-7700-327. <http://www.climb.org.uk>.

United Mitochondrial Disease Foundation. PO Box 1151, Monroeville, PA 15146-1151. (412) 793-8077. Fax: (412) 793-6477. <http://www.umdf.org>.

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Paul A. Johnson

Pyruvate dehydrogenase complex deficiency

Definition

Pyruvate dehydrogenase complex deficiency (PDHA) is a genetic disorder that results in a malfunctioning of the Krebs, or tricarboxylic acid (TCA), cycle. It is sex-linked and appears to be a dominant trait.

Description

PDHA is one of the most common of the **genetic disorders** that cause abnormalities of mitochondrial metabolism. The mitochondria are the organelles inside cells that are reponsible for energy production and respiration at the cellular level. One of the most important processes in the mitochondria is the TCA cycle (also known as the Krebs cycle). The TCA cycle produces the majority of the ATP (chemical energy) necessary for maintenance (homeostasis) of the cell. The production of this ATP is accomplished by chemically converting molecules of the chemical pyruvate into carbon dioxide, water, and ATP. After a blood sugar (glucose) molecule has been broken down into two pyruvate molecules, one of two things will occur: if energy is required by the cell, the molecules will be further broken down into ATP, carbon dioxide, and water; or, if energy is not needed by the cell, the pyruvate molecules will be put back together to

reform a glucose molecule. These transformations of pyruvate are accomplished primarily by two enzymes: pyruvate carboxylase, an enzyme that converts pyruvate molecules into oxaloacetate molecules in preparation to reform glucose molecules; and pyruvate dehydrogenase (PDH), an enzyme that begins the breakdown of the pyruvate into the eventual products of carbon dioxide, water, and ATP. To break down the pyruvate, PDH gets some help from two other enzymes: dihydrolipoyl transacetylase and dihydrolipoyl dehydrogenase. These three enzymes and the five coenzymes (CoA, NAD+, FAD+, lipoic adic, and TPP) that assist these enzymes are collectively known as the pyruvate dehydrogenase complex (PDH complex).

Individuals affected with PDHA have deficiencies in one or more of the three enzymes within the PDH complex. Most have a deficiency of the PDH enzyme itself. Tissues that require the greatest amounts of oxygen (highly aerobic tissues), such as those of the brain and the rest of the central nervous system, are most sensitive to deficiencies in the PDH complex.

People with PDHA have either a complete inability or a severely limited ability to produce PDH. Since these individuals cannot produce the amounts of PDH required to break down pyruvate, the cells cannot produce enough energy, in the form of ATP, to maintain themselves. This causes a progressive degeneration of the tissues, with the most profound effects observed in the brain and central nervous system.

PDH is an enzyme. An enzyme is a chemical that facilitates (catalyzes) the chemical reaction of another chemical or of other chemicals; it is neither a reactant nor a product in the chemical reaction that it facilitates (catalyzes). As a result, enzymes are not used up in chemical reactions; they are recycled. One molecule of an enzyme may be used to facilitate (catalyze) the same chemical reaction over and over again several hundreds of thousands of times. All the enzymes necessary for catalyzing the various reactions of human life are produced within the body by genes. Genetic enzyme deficiency disorders, such as PDHA, result from only one cause: the affected individual cannot produce enough of the necessary enzyme because the **gene** designed to make the enzyme is faulty. Enzymes are not used up in chemical reactions, but they do eventually wear out, or accidentally get expelled. Also, as an individual grows, they may require greater quantities of an enzyme. Therefore, most enzyme deficiency disorders will have a time component to them. Individuals with no ability to produce a particular enzyme may show effects of this deficiency at birth or shortly thereafter. Individuals with only a partial ability to produce a particular enzyme may not show the effects of this deficiency until their need for the enzyme, because of growth or maturation, has outpaced their ability to produce it.

The level of ability of the pyruvate dehydrogenase complex deficiency affected individual to produce PDH, or his or her ability to sustain existing levels of PDH, are the sole determinants of the severity of the observed symptoms in that individual and the age of onset of these symptoms.

PDHA is the most common cause of non-exercise-related build-up of lactic acid in the tissues (primary lactic acidosis). When a tissue requires more energy than it can gain from aerobic processing (TCA cycle), it begins to break down carbohydrates, via an anaerobic process, in order to gain the necessary energy. Lactic acid is the by-product of carbohydrate metabolism. The build-up of lactic acid in the muscle tissues and red blood cells is normal during strenuous exercise. However, the accumulation of lactic acid in other tissues without exercise or without oxygen deprivation is symptomatic of an underlying problem in the normal aerobic process (TCA cycle).

Genetic profile

The gene responsible for PDHA has been mapped to Xp22.2-p22.1. This gene is now termed the PDHA1 gene. At least 50 different mutations of this gene resulting in varying symptoms of PDHA have been identified. Because the gene for PDHA is on the X chromosome, it is called a sex-linked disease. PDHA shows a dominant **inheritance** pattern: therefore, females with only one affected X chromosome also exhibit symptoms of the disease.

Demographics

Almost equal numbers of males and females have been identified as being affected with PDHA. Even though PDHA is known to be transmitted as a sex-linked dominant trait on the X chromosome, it is not necessarily lethal in affected males (who possess only a single X chromosome), because the symptoms of PHDA are quite different depending on the precise mutation responsible for the symptoms in each individual. The genetic mutations are linked to the sex of the affected individual. Affected liveborn males tend to have minor (missense/nonsense type) mutations, while affected females tend to have more major (insertion/deletion type) mutations. The almost unobserved insertion/deletion mutations in males with PDHA suggests that these mutations are fatal to males with only a single X chromosome (homozygous males). Females with two X **chromosomes**, only one of which contains an insertion/deletion type mutation (heterozygous females) and males with an extra X

KEY TERMS

ATP—Adenosine triphosphate. The chemical used by the cells of the body for energy.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Highly aerobic tissues—Tissue that requires the greatest amount of oxygen to thrive.

Hypotonia—Reduced or diminished muscle tone.

Lactic acid—The major by-product of anaerobic (without oxygen) metabolism.

Mitochondria—Organelles within the cell responsible for energy production.

Pyruvate dehydrogenase complex—A series of enzymes and co-factors that allow pyruvate to be converted into a chemical that can enter the TCA cycle.

TCA cycle—Formerly know as the Kreb's cycle, this is the process by which glucose and other chemicals are broken down into forms that are directly useable as energy in the cells.

chromosome (XXY males) with this type of mutation on only one chromosome (heterozygous males) are affected with non-lethal forms of PDHA.

A fixed sequence difference between African and non-African samples of the PDHA1 gene has been identified. That is, those of African descent carry a different version of the PDHA1 gene than those of non-African descent. It has been established that these differences in the subpopulations arose more than 200,000 years ago, which predates the earliest known modern human fossils. This genetic evidence is interesting in that it suggests that the modern human emerged from already genetically divided subpopulations.

Signs and symptoms

PDHA affects primarily the brain and central nervous system. In individuals with extreme deficiencies of PDH, the brain may fail to reach normal size during fetal development leading to a small brain and skull (microcephaly). Abnormal development of the cerebrum, cerebellum, and brainstem are the most common brain dysfunctions associated with PDHA. The normal hollow cavities (ventricles) within the brain are usually much larger than normal (dilated) in individuals affected with PDHA. The connection between the left and right hemispheres of the brain (corpus callosum) is generally underdeveloped or completely absent as well.

A condition in which the normal insulating layer (myelin) that surrounds the neurons is either absent or insufficent (leukodystrophy) is observed in many individuals affected with PDHA. Some PDHA affected individuals also have periods of brain malfunctioning in which the neurons within the cerebellum temporarily lose the ability to act in a coordinated fashion (cerebellar ataxia). These attacks of cerebellar ataxia generally last from a few days to a few weeks and reoccur every three to six months thoughout life with decreasing severity after puberty. Lactic acid accumulation in the brain may also lead to breathing (respiratory) and kidney (renal) problems.

Some individuals affected with PDHA experience increased muscle tone in both legs (spastic diplegia) or in all four limbs (spastic tetraplegia) similar to that seen in the classic case of **cerebral palsy**. Seizures occur in almost all individuals with PDHA. A seizure is the result of sudden abnormal electrical activity in the brain. This electrical activity can result in a wide variety of clinical symptoms including muscle twitches; tongue biting; fixed, staring eyes; a loss of bladder control resulting in involuntary urination; total body shaking (convulsions); and/or loss of consciousness.

Unusual, or dysmorphic, facial features are sometimes associated with PDHA. These include a broad or upturned nose; low-set ears; downward-slanted eyes, drooping eyelids; and a staring or squinting appearance. Other physical symptoms of PDHA include short fingers and arms, urogenital malformations, low muscle tone (hypotonia), and feeding difficulties. Mental impairment is present in some cases. Delayed physical and motor development can also occur.

Diagnosis

Improper brain development in individuals with PDHA is observable in the womb via ultrasound or MRI after birth, although brain malformations may result from any number of other factors. Babies born with PDHA may exhibit low birth weight, a weak suck, failure to thrive, lack of muscle tone, and unusual appearance of the head, face, and limbs. Convulsions, developmental delay, and eye problems may develop a few months after birth. A diagnosis of PDHA is generally confirmed with a blood test for severe lactic acidosis, an observance of deficient PDH activity in sampled or cultured fibroblasts, or by an observance of elevated amounts of lactate and pyruvate in the cerebrospinal fluid drawn in a spinal tap.

Treatment and management

Treatment of PDHA is on a case-by-case basis depending on the observed symptoms. These treatments may include early and continuing intervention programs for developmental delays and mental retardation, anti-convulsants to control seizures, muscle relaxants to control spasticity, and/or surgery to release the permanent muscle, tendon, and ligament tightening (contracture) at the joints that is characteristic of longer term spasticity.

A high fat diet including beer as an alternative source of the chemical acetyl-CoA that is not produced in high enough supply because of the deficiency of PDH enzyme is often recommended for those individuals affected with PDHA. Dietary supplements of thiamine, liproic acid and L-carnitine have also proven beneficial in some cases.

Prognosis

The prognosis for PDHA affected individuals varies widely with the severity of the symptoms. Until gene or enzyme replacement therapy becomes available, the most seriously affected individuals are not likely to receive relief from their symptoms and many will die at early ages. For those less seriously affected, several treatments are available to improve quality of life. Many less severely affected individuals live normal lifespans with their abilities and quality of life only limited by the degree of mental impairment and muscle spasticity that is present.

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United Mitochondrial Disease Foundation. PO Box 1151, Monroeville, PA 15146-1151. (412) 793-8077. Fax: (412) 793-6477. <http://www.umdf.org>.

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Paul A. Johnson

Pyruvate kinase deficiency

Definition

Pyruvate kinase deficiency (PKD) is part of a group of disorders called hereditary nonspherocytic hemolytic anemias. Hereditary nonspherocytic anemias are rare genetic conditions that affect the red blood cells. PKD is caused by a deficiency in the enzyme, pyruvate kinase. Although PKD is the second most common of the hereditary nonspherocytic anemias, it is still rare, with the incidence estimated to be 51 cases per million in the Caucasian population.

Description

In PKD, there is a functional abnormality with the enzyme pyruvate kinase. Usually, pyruvate kinase acts as a catalyst in the glycolysis pathway, and is considered an essential component in this pathway. Glycolysis is the method by which cells produce their own energy. A problem with any of the key components in glycolysis can alter the amount of energy produced. In the red blood cells, glycolysis is the only method available to produce energy. Without the proper amount of energy, the red blood cells do not function normally. Since pyruvate kinase is one of the key components in glycolysis, when there is a problem with this enzyme in the red blood cells, there is a problem with the production of energy, causing the red blood cells to not function properly.

There are four different forms of the pyruvate kinase enzyme in the human body. These forms, called isozymes, all perform the same function but each isozyme of pyruvate kinase is structurally different and works in different tissues and organs. The four isozymes of pyruvate kinase are labeled M1, M2, L, and R. The isozyme M1 is found in the skeletal muscle and brain, isozyme M2 can be found in most fetal and adult tissues, isozyme L works in the liver, and isozyme R works in the

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Catalyst—A substance that changes the rate of a chemical reaction, but is not physically changed by the process.

Compound heterozygotes—Having two different mutated versions of a gene.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Glycolysis—The pathway in which a cell breaks down glucose into energy.

Hemolytic anemia—Anemia that results from premature destruction and decreased numbers of red blood cells.

Heterozygote—Having two different versions of the same gene.

Homozygote—Having two identical copies of a gene or chromosome.

Isozyme/Isoenzyme—A group of enzymes that perform the same function, but are different from one another in their structure or how they move.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nonspherocytic—Literally means not sphere-shaped. Refers to the shape of red blood cells in nonspherocytic hemolytic anemia.

red blood cells. In PKD, only the pyruvate kinase isozyme found in red blood cells, called PKR, is abnormal. Therefore, PKD only affects the red blood cells and does not directly affect the energy production in the other organs and tissues of the body.

Genetic profile

There are two PK genes and each **gene** produces two of the four isozymes of pyruvate kinase. The M1 and M2 isozymes are produced by the pyruvate kinase gene called PKM2 and pyruvate kinase isozymes, L and R, are products of the pyruvate kinase gene, PKLR. The PKLR gene is located on chromosome 1, on the q arm (the top half of the chromosome), in region 21 (written as 1q21). As of 2001, there have been over 125 different mutations described in the PKLR gene that have been detected in individuals with PKD.

PKD is mainly inherited in an autosomal recessive manner. There have been a few families where it appeared that PKD was inherited in either an autosomal dominant manner or where the carriers of PKD exhibited mild problems with their red blood cells. As with all autosomal recessive conditions, affected individuals have a mutation in both pair of genes. Most individuals with PKD are compound heterozygotes, meaning that each PKLR gene in a pair contains a different mutation. There are individuals who have the same mutation on each PKLR gene, but these individuals tend to be children of parents who are related to each other.

There are three mutations in the PKLR gene called, 1529A, 1456T, and 1468T, that are seen more frequently in individuals with PKD than the other mutations. The mutation 1529A is most frequently seen in Caucasians of northern and central European descent and is the most common mutation seen in PKD. The mutation 1456T is more common in individuals of southern European descent and the mutation 1468T is more common in individuals of Asian descent.

For most of the mutations seen in the PKLR gene, no correlation between the specific mutation and the severity of the disorder has been observed. However, for two of the mutations, there has been speculation on their affect on the severity of PKD. When the mutation 1456T has been seen in the homozygous state (when both PKLR genes contain the same mutation), those rare individuals experienced very mild symptoms of PKD. Also, there have been individuals who were homozygous for the 1529A mutation. These individuals had a very severe form of PKD. Therefore, it is thought that the 1456T mutation is associated with a milder form of the disease and the 1529A mutation is associated with a more severe form of the disease. It is not known how these mutations affect the severity of PKD when paired with different mutations.

Demographics

In general, PKD not does appear to affect one gender more than another or be more common in certain regions. However, there are studies of an Amish group in Pennsylvania where a severe form of PKD is more common. As previously mentioned, the three mutations found in the PKLR gene have been linked to individuals of specific decents. Caucasians of northern and central

European decent are more likely to have the 1529A mutations, individuals of southern European descent usually have the 1456T mutation, and individuals of Asian descent are more likely to have the 1468T mutation.

Signs and symptoms

In general, the more severe the PKD, the earlier in life symptoms tend to be detected. Individuals with the more severe form of PKD often show symptoms soon after birth, but most individuals with PKD begin to exhibit symptoms during infancy or childhood. In individuals with the more mild form of PKD, the condition is sometimes not diagnosed until late adulthood, after an acute illness, or during a pregnancy evaluation.

Symptoms of PKD are similar to those symptoms seen in individuals who have long-term hemolytic anemia. The more common symptoms include variable degrees of jaundice (a yellowish pigment of the skin), slightly to moderately enlarged spleen (splenomegaly), and increased incidence of gallstones. Other physical effects of PKD can include smaller head size and the forehead appearing prominent and rounded (called frontal bossing). If a child with PKD has their spleen removed, their growth tends to improve. Even within the same family, individuals can have different symptoms and severity of PKD.

In individuals with PKD, the red blood cells are taken out of their circulation earlier than normal (shorter life span). Because of this, individuals with PKD will have hemolytic anemia. Additionally, the anemia or other symptoms of PKD may worsen during a sudden illness or pregnancy.

Diagnosis

A diagnosis of PKD can be made by measuring the amount of pyruvate kinase in red blood cells. Individuals with PKD tend to have 5–25% of the normal amount of pyruvate kinase. Carriers of PKD also can have less pyruvate kinase in their red blood cells, approximately 40–60% of the normal value. However, there is an overlap between the normal range of pyruvate kinase and the ranges seen with carriers of PKD. Therefore, measuring the amount of pyruvate kinase in the red blood cells is not a good method of detecting carriers of PKD. If the mutations causing PKD in a family are known, it may be possible to perform mutation analysis to determine carrier status of an individual and to help diagnose individuals with PKD.

Treatment and management

In the severest cases, individuals with PKD will require multiple blood transfusions. In some of those cases, the spleen may be removed (splenectomy). Red blood cells are normally removed from circulation by the spleen. By removing an individual's spleen (usually a child), the red blood cells are allowed to stay in circulation longer than normal; thereby reducing the severity of the anemia. After a splenectomy, or once an individual with PKD is older, the number of transfusions tends to decrease.

Prognosis

The prognosis of PKD is extremely variable. Early intervention and treatment of symptoms frequently improve the individual's health. Without treatment, individuals may experience severe complications that could become fatal. Individuals with a mild form of PKD may appear to have no symptoms at all.

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Sharon A. Aufox, MS, CGC

R

Rapp-Hodgkin syndrome *see* **Ectodermal dysplasia**

Raynaud disease

Definition

Raynaud disease refers to a disorder in which the fingers or toes (digits) suddenly experience decreased blood circulation. It is characterized by repeated episodes of color changes of the skin of digits during cold exposure or emotional stress.

Description

Raynaud disease can be classified as one of two types: primary (or idiopathic) and secondary (also called Raynaud's phenomenon). Primary Raynaud disease has no predisposing factor, is more mild, and causes fewer complications. About half of all cases of Raynaud disease are of this type. Women are five times more likely than men to develop primary Raynaud disease. The average age of diagnosis is between 20 and 40 years. Approximately three out of ten people with primary Raynaud disease eventually progress to secondary Raynaud disease after diagnosis. About 15% of individuals improve.

Secondary Raynaud disease is the same as primary Raynaud disease, but occurs in individuals with a predisposing factor, usually a form of collagen vascular disease. What is typically identified as primary Raynaud may be later identified as secondary once a predisposing disease is diagnosed. This occurs in approximately 30% of patients. As a result of the predisposing disease, the secondary type is often more complicated and severe, and is more likely to worsen.

Several related conditions that predispose persons to secondary Raynaud disease include **scleroderma**, lupus erythematosus, rheumatoid arthritis, and polymyositis. Pulmonary hypertension and some nervous system disorders such as herniated discs and tumors within the spinal column, strokes, and polio can progress to Raynaud disease. Finally, injuries due to mechanical trauma caused by vibration (such as that associated with chain saws and jackhammers), repetitive motion (carpal tunnel syndrome), electrical shock, and exposure to extreme cold can led to the development of Raynaud disease. Some drugs used to control high blood pressure or migraine headaches have been known to cause Raynaud disease.

Genetic profile

There is significant familial aggregation of primary Raynaud disease. However, as of 2001, no causative **gene** has been identified.

Risk factors for Raynaud disease differ between males and females. Age and smoking seem to be associated with Raynaud disease only in men, while the associations of marital status and alcohol use with Raynaud disease are usually only observed in women. These findings suggest that different mechanisms influence the expression of Raynaud disease in men and women.

Demographics

The prevalence of Reynaud phenomena in the general population varies from 4–15%. Females are seven times more likely to develop Raynaud diseases than are men. The problem has not been correlated with coffee consumption, dietary habits, occupational history (excepting exposure to vibration), or exposure to most drugs. An association between Raynaud disease and migraine headaches has been reported. Secondary Raynaud disease is common among individuals with systemic lupus erythematosus in tropical countries.

Signs and symptoms

Both primary and secondary Raynaud disease signs and symptoms are thought to be due to arterioles

KEY TERMS

Arteriole—The smallest type of artery.

Artery—A blood vessel that carries blood away from the heart to peripheral tissues.

Gangrene—Death of a tissue, usually caused by insufficient blood supply and followed by bacterial infection of the tissue.

Idiopathic—Of unknown origin.

Lupus erythematosus—A chronic inflammatory disease that affects many tissues and parts of the body including the skin.

Polymyositis—An inflammation of many muscles.

Pulmonary hypertension—A severe form of high blood pressure caused by diseased arteries in the lung.

Rheumatoid arthritis—Chronic, autoimmune disease marked by inflammation of the membranes surrounding joints.

Scleroderma—A relatively rare autoimmune disease affecting blood vessels and connective tissue that makes skin appear thickened.

over-reacting to stimuli. Cold normally causes the tiny muscles in the walls of arteries to contract, thus reducing the amount of blood that can flow through them. In people with Raynaud disease, the extent of constriction is extreme, thus severely restricting blood flow. Attacks or their effects may be brought on or worsened by anxiety or emotional distress.

There are three distinct phases to an episode of Raynaud disease. When first exposed to cold, small arteries respond with intense contractions (vasoconstriction). The affected fingers or toes (in rare instances, the tip of the nose or tongue) become pale and white because they are deprived of blood and, thus, oxygen. In response, capillaries and veins expand (dilate). Because these vessels are carrying deoxygenated blood, the affected area then becomes blue in color. The area often feels cold and tingly or numb. After the area begins to warm up, the arteries dilate. Blood flow is significantly increased. This changes the color of the area to a bright red. During this phase, persons often describe the affected area as feeling warm and throbbing painfully.

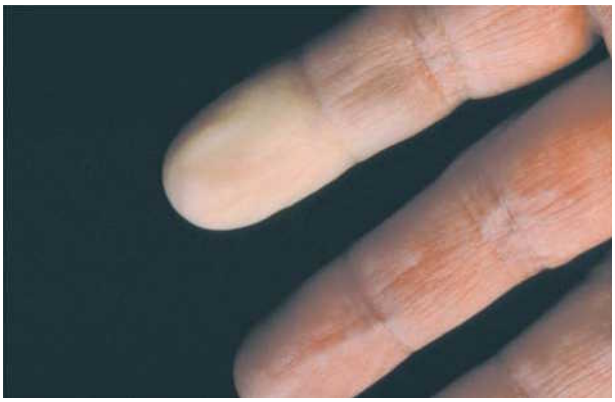
Raynaud disease may initially affect only the tips of fingers or toes. As the disease progresses, it may eventually involve all of one or two digits. Ultimately, all the fingers or toes may be affected. About one person in ten will experience a complication called sclerodactyly. In sclerodactyly, the skin over the involved digits becomes tight, white, thick, smooth, and shiny. In approximately 1% of cases of Raynaud disease, deep sores (ulcers) may develop in the skin. In rare cases of frequent, repetitive bouts of severe ischemia (decreased supply of oxygenated blood to tissues or organs), tissue loss, or gangrene, may result and amputation may be required.

Diagnosis

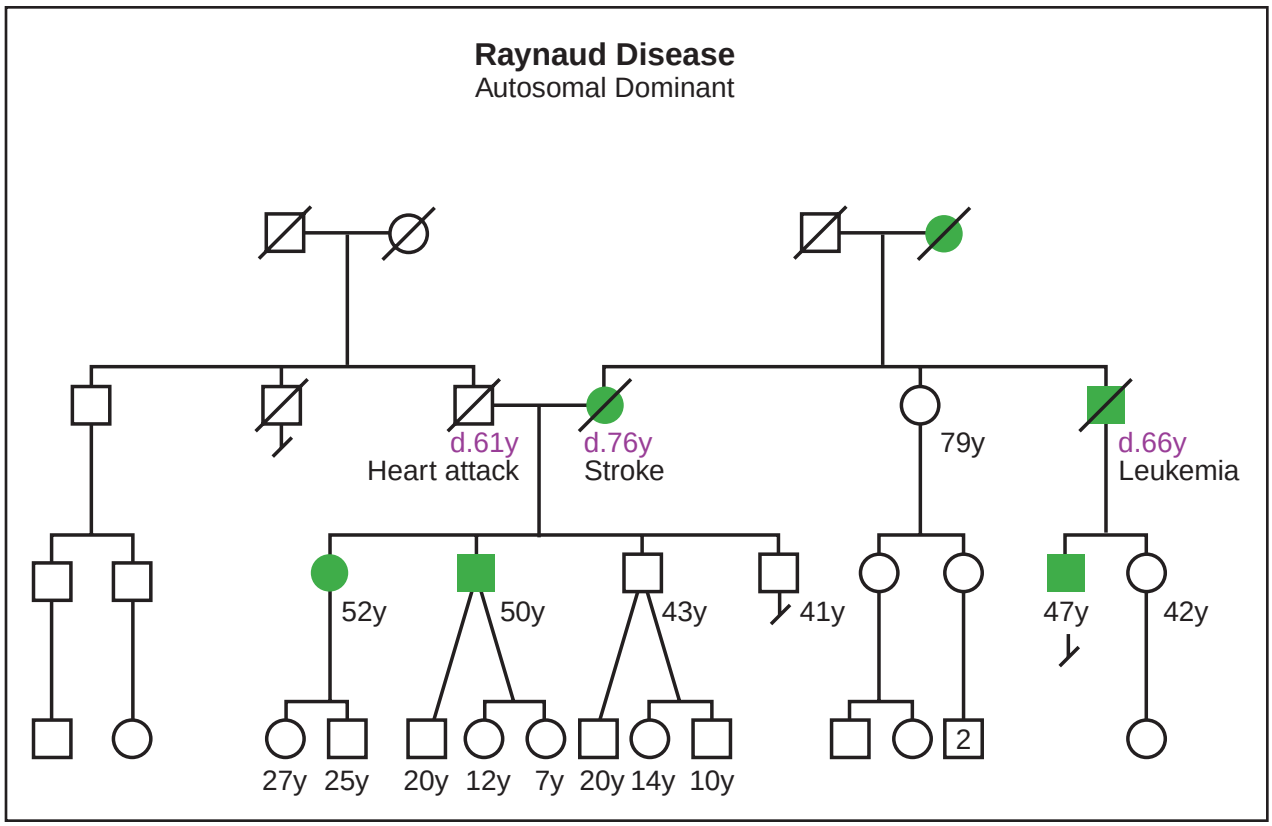
Primary Raynaud disease is diagnosed following the Allen Brown criteria. There are four components. The certainty of the diagnosis and severity of the disease increase as more criteria are met. The first is that at least two of the three color changes must occur during attacks provoked by cold and/or stress. The second is that episodes must occur periodically for at least two years. The third is that attacks must occur in both the hands and the feet in the absence of vascular occlusive disease. The last is that there is no other identifiable cause for the Raynaud episodes.

A cold stimulation test may also be performed to help to confirm a diagnosis of Raynaud disease. The temperature of affected fingers or toes is taken. The hand or foot is then placed completely into a container of ice water for 20 seconds. After removal from the water, the temperature of the affected digits is immediately recorded. The temperature is taken every five minutes until it returns to the pre-immersion level. Most individuals recover normal temperature within 15 minutes. People with Raynaud disease may require 20 minutes or more to reach their pre-immersion temperature.

Laboratory testing is performed frequently. However, these results are often inconclusive for several rea-



A phenomenon of Raynaud disease occurs when blood flow is temorarily interrupted, causing extremities to become pale due to poor blood circulation. *(Custom Medical Stock Photo, Inc.)*



(Gale Group)

sons. Provocative testing such as the ice immersion just described, is difficult to interpret because there is considerable overlap between normal and abnormal results. The antinuclear antibody test of blood is usually negative in Raynaud disease. Capillary beds under fingernails usually appear normal. Erythrocyte sedimentation rates are often abnormal in people with connective tissue diseases. Unfortunately, this finding is not consistent in people with Raynaud disease.

Treatment and management

There is no known way to prevent the development of Raynaud disease. Further, there is no known cure for this condition. Therefore, avoidance of the trigger is the best supportive management available. Most cases of primary Raynaud disease can be controlled with proper medical care and avoidance.

Many people are able to find relief by simply adjusting their lifestyles. Affected individuals need to stay warm and keep their hands and feet well covered in cold weather. Layered clothing, scarves, heavy coats, heavy socks, and mittens over gloves are suggested because gloves alone allow heat to escape. It is also recommended that patients cover or close the space between their sleeves and mittens. Indoors, they should wear socks and comfortable shoes. Excessive emotional stress should be avoided. Smokers should quit as nicotine worsens the problem. The use of vibrating tools should be avoided as well.

Biofeedback has been used with some success in treating primary Raynaud. This involves teaching people to "think" their fingers and toes to be warm by willing blood to flow through affected arterioles. Biofeedback has had only limited success. Occasionally, medications such as calcium-channel blockers, reserpine, or nitroglycerin may be prescribed to relax artery walls and improve blood flow.

Because episodes of Raynaud disease have also been associated with stress and emotional upset, the condition may be improved by learning to manage stress. Regular exercise is known to decrease stress and lower anxiety. Hypnosis, relaxation techniques, and visualization are also useful methods to help control emotions.

Biofeedback training is a technique during which a patient is given continuous information on the temperature of his or her digits, and then taught to voluntarily

control this temperature. Some alternative practitioners believe that certain dietary supplements and herbs may be helpful in decreasing the vessel spasm of Raynaud disease. Suggested supplements include vitamin E (found in fruits, vegetables, seeds, and nuts), magnesium (found in seeds, nuts, fish, beans, and dark green vegetables), and fish oils. The circulatory herbs cayenne, ginger, and prickly ash may help enhance circulation to affected areas.

Prognosis

The prognosis for most people with Raynaud disease is very good. In general, primary Raynaud disease has the best prognosis, with a relatively small chance (1%) of serious complications. Approximately half of all affected individuals do well by taking simple precautions, and never require medication. The prognosis for people with secondary Raynaud disease (or phenomenon) is less predictable. This prognosis depends greatly on the severity of other associated conditions such as scleroderma, lupus, or Sjögren syndrome.

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American Heart Association. 7272 Greenville Ave., Dallas, TX 75231-4596. (214) 373-6300 or (800) 242-8721. inquire @heart.org. <http://www.americanheart.org>.

Irish Raynaud's and Scleroderma Society. PO Box 2958 Foxrock, Dublin 18, Ireland. (01) 235 0900. irss@indigo.ie.

National Heart, Lung, and Blood Institute. PO Box 30105, Bethesda, MD 20824-0105. (301) 592-8573. nhlbiinfo @rover.nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Raynaud's & Scleroderma Association (UK). 112 Crewe Road, Alsager, Cheshire, ST7 2JA, UK. (44) (0) 1270 872776. webmaster@raynauds.demon.co.uk. <http://www.raynauds.demon.co.uk>.

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L. Fleming Fallon, Jr., MD, PhD, DrPH

Recurrent polyserositis *see* **Familial mediterranean fever**

Refsum disease

Definition

Refsum disease is an inherited disorder in which the enzyme responsible for processing phytanic acid is defective. Accumulation of phytanic acid in the tissues and the blood leads to damage of the brain, nerves, eyes, skin, and bones.

Description

Refsum disease was first characterized by the Norwegian physician, Sigvald Refsum, in the 1940s and is known by other names, such as classical Refsum disease, adult Refsum disease, phytanic acid alpha-hydroxylase deficiency, phytanic acid storage disease, hypertrophic neuropathy of Refsum, heredopathia atactica polyneuritiformis, and hereditary motor and sensory neuropathy IV. Refsum disease should not be confused with **infantile Refsum disease**, which was once thought to be a variant of the disorder but is now known to be a genetically and biochemically distinct entity. Sometimes infantile Refsum disease is simply referred to as "Refsum disease," furthering the confusion.

Living bodies are made up of millions of individual cells that are specifically adapted to carry out particular functions. Within cells are even smaller structures, called organelles, that perform jobs and enable the cell to serve

its ultimate purpose. One type of organelle is the peroxisome, whose main function is to break down waste materials or to process materials that, if allowed to accumulate, would prove toxic to the cells.

Phytanic acid is a substance found in foods, such as dairy products, beef, lamb, and some fish. Normally, phytanic acid is processed by a set of enzymes within the cell to convert it to another form. In the past, scientists were unsure where in the cell this process took place, hypothesizing that it may occur in the peroxisome or another organelle, called the mitochondrion. However, recent research has definitively determined that the enzymes responsible for processing phytanic acid are located in the peroxisome.

Refsum disease is an inherited disorder in which one of the peroxisomal enzymes, phytanic acid hydroxylase (also called phytanic acid oxidase, or phytanyl CoA hydroxylase), is defective, resulting in unprocessed phytanic acid. Consequently, high levels of phytanic acid build up in the tissues of the body and the bloodstream, causing damage to different organ systems.

Genetic profile

Refsum disease is a genetic condition and can be inherited or passed on in a family. The genetic defect for the disorder is inherited as an autosomal recessive trait, meaning that two abnormal genes are needed to display the disease. A person who carries one abnormal **gene** does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to his or her children. A child must inherit the same abnormal gene from each parent to display the disease.

Refsum disease is caused by a deficiency in an enzyme, phytanic acid hydroxylase. The gene encoding for this enzyme, called PAHX or PHYH, was identified in 1997 and mapped to human chromosome 10 (locus: 10pter-p11.2). Several common mutations have been identified in the gene that result in Refsum disease.

Demographics

Refsum disease is rare, but the exact incidence and prevalence of the disorder in the general population is not known. Refsum disease may not be distributed equally among geographical areas or different ethnic groups, as most of the diagnosed cases have been found in children and young adults of Scandinavian heritage.

Signs and symptoms

Patients with Refsum disease generally do not show obvious defects at birth, and growth and development initially appears normal. The onset of clinical symptoms varies from early childhood to age 50, but symptoms usually appear before 20 years of age. The manifestations of Refsum disease primarily involve the nervous system, the

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Cerebellar ataxia—Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Ichthyosis—Rough, dry, scaly skin that forms as a result of a defect in skin formation.

Mutant—A change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease.

Organelle—Small, sub-cellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

Peripheral neuropathy—Any disease of the nerves outside of the spinal cord, usually resulting in weakness and/or numbness.

Peroxisome—A cellular organelle containing different enzymes responsible for the breakdown of waste or other products.

Phytanic acid—A substance found in various foods that, if allowed to accumulate, is toxic to various tissues. It is metabolized in the peroxisome by phytanic acid hydroxylase.

Phytanic acid hydroxylase—A peroxisomal enzyme responsible for processing phytanic acid. It is defective in Refsum disease.

Plasmapheresis—A procedure in which the fluid component of blood is removed from the bloodstream and sometimes replaced with other fluids or plasma.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

eye, the skin, the bones, and, in rare cases, the heart and kidneys.

Phytanic acid deposits in the fatty sheaths surrounding nerves, causing damage and resulting in peripheral neuropathy in 90% of patients with Refsum disease. Peripheral neuropathy is the term for dysfunction of the nerves outside of the spinal cord, causing loss of sensation, muscle weakness, pain, and loss of reflexes. Nerves leading to the nose and ears can also be affected, resulting in anosmia (loss of the sense of smell) in 35% of patients and hearing loss or deafness in 50% of patients. Finally, Refsum disease results in cerebellar ataxia in 75% of patients. Cerebellar ataxia is a defect in a specific part of the brain (the cerebellum), resulting in loss of coordination and unsteadiness. In contrast to infantile Refsum disease, people with Refsum disease do not show mental retardation and generally have normal intelligence.

Accumulation of phytanic acid also results in disorders of the eye. The most common finding is **retinitis pigmentosa**, a degeneration of the retina resulting in poor nighttime vision and sometimes blindness. Disorders of pupil movement and nystagmus (uncontrollable movements of the eye) may also be present due to related nervous system damage. Other eye manifestations of Refsum disease may include **glaucoma** (abnormally high pressure in the eye, leading to vision loss) and cataracts (clouding of the lens of the eye).

People with Refsum disease often develop dry, rough, scaly skin. These skin changes, called **ichthyosis**, can occur over the entire body, but sometimes will appear only on the palms and soles of the feet. In addition to these skin abnormalities, 60% of affected people may experience abnormal bone growth, manifesting as shortened limbs or fingers, or abnormal curvatures of the spine.

Patients with Refsum disease usually first present to a physician complaining of weakness in the arms and legs, physical unsteadiness and/or nightblindness or failing vision. The symptoms associated with Refsum disease are progressive and, if untreated, will become more numerous and severe as the patient ages. For reasons that are not completely understood, clinical deterioration can be sometimes be interrupted by periods of good health without symptoms.

Diagnosis

Refsum disease is diagnosed though a combination of consistent medical history, physical exam findings, and laboratory and **genetic testing**. When patients with Refsum disease present to their physicians complaining of visual problems or muscle weakness, physical signs of retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, or skin and bone changes (as discussed above) are often noted. These findings raise suspicion for a genetic syndrome or metabolic disorder, and further tests are conducted.

Laboratory tests reveal several abnormalities. Normally, phytanic acid levels are essentially undetectable in the plasma. Thus, the presence of high levels of phytanic acid in the bloodstream is highly indicative of Refsum disease. If necessary, a small portion of the patient's connective tissue can be sampled and grown in a laboratory and tested to demonstrate a failure to process phytanic acid appropriately. Other associated laboratory abnormalities include the presence of high amounts of protein in the fluid that bathes the spinal cord, or abnormal electrical responses recorded from the brain, muscles, heart, ears, retina, and various nerves as a result of nervous system damage.

Genetic testing can also be performed. When a diagnosis of Refsum disease is made in a child, genetic testing of the PAHX/PHYH gene can be offered to determine if a specific gene change can be identified. If a specific change is identified, carrier testing can be offered to relatives. In families where the parents have been identified to be carriers of the abnormal gene, diagnosis of Refsum disease before birth is possible. Prenatal diagnosis is performed on cells obtained by **amniocentesis** (withdrawal of the fluid surrounding a fetus in the womb using a needle) at about 16–18 weeks of pregnancy or from the chorionic villi (a part of the placenta) at 10–12 weeks of pregnancy.

Treatment and management

There is no cure for Refsum disease, thus treatment focuses on reducing levels of phytanic acid in the bloodstream to prevent the progression of tissue damage. Phytanic acid is not made in the human body and comes exclusively from the diet. Restriction of phytanic acid-containing foods can slow progress of the disease or reverse some of the symptoms. Patients are advised to maintain consumption of phytanic acid below 10 mg/day (the normal intake is approximately 100 mg/day). Sources of high levels of phytanic acid to be avoided include meats (beef, lamb, goat), dairy products (cream, milk, butter, cheese), and some fish (tuna, cod, haddock). Plasma levels of phytanic acid can be monitored periodically by a physician to investigate the effectiveness of the restricted diet and determine if changes are required. As a result of dietary restriction, nutritional deficiencies may result. Consultation with a nutritionist is recommended to assure proper amounts of calories, protein, and vitamins are obtained through the diet, and nutritional supplements may be required.

Because phytanic acid is stored in fat deposits within the body, it is important for patients with Refsum disease to have regular eating patterns; with even brief periods of

fasting, fat stores are converted to energy, resulting in the release of stored phytanic acid into the blood stream. Thus, unless a patient assumes a regular eating pattern, repeated and periodic liberation of phytanic acid stores results in greater tissue damage and symptom development. For these same reasons, intentional weight loss though calorie-restricted diets or vigorous exercise is discouraged.

Another useful adjunct to dietary treatment is plasmapheresis. Plasmapheresis is a procedure by which determined amounts of plasma (the fluid component of blood that contains phytanic acid) is removed from the blood and replaced with fluids or plasma that do not contain phytanic acid. Regular utilization of this technique allows people who fail to follow a restricted diet to maintain lower phytanic acid levels and experience less tissue damage and symptoms.

Patients with Refsum disease should be seen regularly by a multidisciplinary team of health care providers, including a pediatrician, neurologist, ophthalmologist, cardiologist, medical geneticist specializing in metabolic disease, nutritionist, and physical/occupational therapist. People with Refsum disease, or those who are carriers of the abnormal gene or who have an relative with the disorder, can be referred for **genetic counseling** to assist in making reproductive decisions.

Prognosis

The prognosis of Refsum disease varies dramatically. The disorder is slowly progressive and, if left untreated, severe symptoms will develop with considerably shortened life expectancy. However, if diagnosed early, strict adherence to a phytanic acid-free dietary regimen can prevent progression of the disease and reverse skin disease and some of the symptoms of peripheral neuropathy. Unfortunately, treatment cannot undo existing damage to vision and hearing.

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Oren Traub, MD, PhD

Refsum disease, infantile form *see* **Infantile refsum disease**

Reis-Pucklers corneal dystrophy *see* **Corneal dystrophy**

Renal failure due to hypertension

Definition

Renal failure (kidney failure) is caused primarily by chronic high blood pressure (hypertension) over many years. Hypertension is the second major cause, after diabetes, of end stage renal disease (ESRD) and is responsible for 25–30% of all reported cases. In addition, many people with diabetes also have hypertension, thus high blood pressure plays an even larger role in kidney failure.

Description

About 398,000 people were diagnosed with end-stage renal disease in 1998. Of these, about 83,000 had hypertension and about 133,000 had diabetes. That same year, approximately 63,000 people with ESRD passed away. Most people with ESRD have had symptoms for a long time and may have had kidney disease (nephropathy) for as many as 20 years or more prior to experiencing kidney failure.

Genetic profile

It is believed that most cases of hypertension leading to kidney failure have a genetic element. Finding a genetic link is complicated by the fact that nearly half of all people with renal failure have three or more serious disorders, such as diabetes. Animal studies have been done to find genetic linkages to hypertension and kidney failure, but genetic studies on humans are in their infancy. A recent breakthrough came in a study of African American subjects with hypertensive end-stage renal disease. Researchers found a significant association between severe hypertension and mutations on the HSD11B2 **gene**. This is a gene that plays a role in sodium retention and related factors. Their data suggested that the 16q22.1 chromosome region was the location of the mutation.

In another study, researchers studied an Israeli family of Iraqi-Jewish origin whose members suffered from hypertension and renal failure. The researchers found a genetic locus at 1q21 that was autosomal dominant. They also hypothesized that the gene encoding atrial natriutetic

KEY TERMS

Dialysis—Process by which special equipment purifies the blood of a patient whose kidneys have failed.

Nephropathy—Kidney disease.

Proteinuria—Excess protein in the urine.

Serum creatinine—A chemical in the urine of kidney patients used to determine kidney disease and failure. Elevated levels of serum creatinine are an early marker for severe kidney disease or failure.

Transplantation—The implanting of an organ from either a deceased person (cadaver) or from a live donor to a person whose organ has failed.

peptide receptor-1 (NPR1) was the disease gene that led to the hypertension/renal failure.

Other families with high rates of hypertension have also been studied. For example, researchers observed a family of Old Order Amish in Lancaster, Pennsylvania and found a genetic link for hypertension to chromosome 2q31-34. The subjects were not experiencing kidney failure, thus, further study would be needed to determine if the identified genetic locus also coded for ESRD.

Demographics

People of all ages, races, and both sexes may develop kidney failure due to hypertension. However, some groups are at much greater risk than others. African Americans are at particularly high risk for both hypertension and renal failure and have four times the number of ESRD cases as Caucasians. They also experience kidney failure at a younger age, with an onset at about age 56 compared to an onset at age 62 for Caucasians. African Americans also have a higher rate of diabetes than non-African Americans, another reason for their increased risk for kidney failures. Native Americans and Alaskan Natives are also at high risk for ESRD. There are about the same number of males and females with newly diagnosed ESRD.

In general, according to the National Institutes of Health, the risk for ESRD increases with age, and those who are over age 65 are at greatest risk for ESRD. The United States Renal Data Service (USRDS) of the National Institutes of Health tracks kidney failure statistics in the United States. According to the USRDS, in 1998, the rate of new cases for those under age 20 was just 13 per million, and the rate increased to 109 for those ages 20–44. A sharp upturn of five times that rate occurred in the 45–64 age group, when the rate is 545 per million people. The rate for those over 65 is about double, at 1,296 per million people. The mean age for individuals with ESRD was 62 years in 1998.

Signs and symptoms

Universal symptoms of ESRD are severe fatigue, fluid retention (edema), and elevated blood pressure readings. Other symptoms include a failure to eat (anorexia) and skin color changes such as a change to a yellow-brown skin color. Urea from perspiration may appear on the skin as whitish crystals, similar to frost. Pruritis (severe itching of the skin) is common. Patients may have muscle cramps and convulsions. Many have malnutrition from anorexia and vomiting. Gastric ulcers are common, as are cardiac symptoms stemming from the retention of sodium and water. Anemia (low levels of iron in the blood) is also common.

Diagnosis

Diagnosis is based on the results of a physical examination and laboratory blood and urine tests. A patient who has end stage renal disease looks very ill and has obvious fluid retention and clear indicators of severe disease. Anemia is common. Blood pressure is elevated, and even patients who did not have hypertension prior to the onset of ESRD will develop hypertension. Patients also usually have massive amounts of protein in the urine and high levels of serum creatinine. Urea levels are also raised.

Treatment and management

Once physicians diagnose end stage renal disease, they must make a plan for dialysis. In addition, patients may be placed on restricted fluids. Anemia is treated and transfusions are given if anemia is severe. ACE inhibitor drugs may be prescribed at low doses to treat cardiac symptoms. Diuretics may be prescribed to reduce fluid retention. Multivitamins may be recommended because of food restrictions.

All patients with kidney failure, despite the cause of the failure, must receive kidney dialysis or kidney transplantation. Eventually, those on dialysis will require transplantation of a kidney, either from a recently deceased person or a live donor. (Each person has two kidneys and can live normally with only one kidney.) About 13,000 kidney transplants are performed in the United States each year and about 47,000 people wait for a donated kidney per year.

There are two types of dialysis. The most common type of treatment is “hemodialysis,” a procedure that uses

a machine called a dialyzer to clean and filter the blood, since the kidneys can no longer perform that function. A connection from the machine is made to the patient's bloodstream and the blood travels through the dialyzer where it is cleaned for 2–4 hours. This procedure is generally performed three times a week. Patients must also change their diets to carefully limit the amount of salt, potassium, and fluids that are consumed, among other dietary restrictions that are given.

Peritoneal dialysis is another option for patients with kidney failure. In this procedure, the patient's own abdominal lining (the peritoneal membrane) is used to help clean the blood. Rather than the patients own blood traveling to a machine, as with a dialyzer, a cleansing solution is transferred through a special tube (catheter) directly into the body. The catheter remains in the body. The number of treatments and time to perform the cleansing procedures vary.

Prognosis

Most patients will eventually need a transplanted kidney to continue to live. The survival rate for those on kidney dialysis after one year is about 80% and after two years, about 66%. However, the five year survival rate with dialysis is 29% and the 10 year survival rate is only 8%.

In contrast, the survival rate for those who receive a transplanted kidney from a deceased person is 94% after one year, 92% after two years and 80% after five years. The 10 year survival rate with a cadaver transplantation is 57%. The survival rates are higher when the kidney is from a live donor; for example, the survival rate after 5 years with a live donor kidney is 89% and about 77% after 10 years.

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ORGANIZATIONS

American Association of Kidney Patients. 100 S. Ashley Dr., Suite 280, Tampa, FL 33602. (800) 749-2257. <www.aakp.org>.

American Kidney Fund. Suite 1010, 6110 Executive Blvd., Rockville, MD 20852. (899) 638-8299.

National Kidney and Urologic Disases Information Clearinghouse. 3 Information Way, Bethesda, MD 20892-3560.

National Kidney Foundation. 30 East 33rd St., New York, NY 10016. (800) 622-9010. <http://www.kidney.org>.

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Christine Adamec

Renpenning syndrome

Definition

Renpenning syndrome is an inherited X-linked disorder that manifests itself in males. It is characterized by mental retardation, short stature, a smaller than normal head circumference (microcephaly), and small testes. The syndrome was first described by Hans Renpenning, in 1962, in a large Mennonite family living in Manitoba, Canada. The term "Renpenning syndrome" came to be used as a general designation for X-linked mental retardation. However, as the syndrome has been mapped to Xp11.2-p11.4, the term "Renpenning syndrome" should be limited to the condition that maps to this region and is characterized by severe mental retardation, microcephaly, short stature, and small testes. The prevalence is unknown.

Description

Renpenning syndrome is among the group of **genetic disorders** known as X-linked mental retardation (XLMR) syndromes. Developmental delay is present early with males learning to walk at age 2–3 years and able to say simple words at age 3–4 years. Although an affected male may appear physically normal, his head circumference and height will be at the lower limits of normal. After puberty, testes will be smaller than normal.

KEY TERMS

Microcephaly—An abnormally small head.

Renpenning syndrome—X-linked mental retardation with short stature and microcephaly not associated with the fragile X chromosome and occurring more frequently in males, although some females may also be affected.

Short stature—Shorter than normal height, can include dwarfism.

Small testes—Refers to the size of the male reproductive glands, located in the cavity of the scrotum.

X-linked mental retardation—Subaverage general intellectual functioning that originates during the developmental period and is associated with impairment in adaptive behavior. Pertains to genes on the X chromosome.

Diagnosis is very difficult especially if there is only one male with mental retardation in a family. The diagnosis is exclusively based on evidence of **inheritance** of the above clinical findings in an X-linked manner and localization to the short arm (Xp11.1-p11.4) of the X chromosome.

Genetic profile

Renpenning syndrome is caused by an alteration in an unknown **gene** located on the short arm (Xp11.2-p11.4) of the X chromosome. The altered gene in affected males is inherited, in most cases, from a carrier mother. Since males have only one X chromosome, a **gene mutation** on the X is fully expressed in males. Carrier females, with one normal X chromosome and one affected X chromosome, do not have any of the phenotype associated with Renpenning syndrome.

Female carriers have a 50/50 chance of transmitting the altered gene to a daughter or a son. A son inheriting the altered gene will have Renpenning syndrome. The affected son will likely not reproduce.

Demographics

Only males are affected with Renpenning syndrome. Carrier females do not express any of the signs or symptoms. Although Renpenning syndrome has been reported in a single Canadian family, it is believed to be present in all racial/ethnic groups.

Signs and symptoms

Manifestations of Renpenning syndrome may be present at birth. One male was reported to have global developmental delay at birth. All affected males had delay in reaching developmental milestones—walking by 18–24 months and having little or no speech by age three.

Affected males have a small head circumference (microcephaly), are of short stature, and have small testes. Facial features may include central balding, an upslant to the eye openings, and a short distance between the nose and the upper lip. Other clinical findings present in some of the affected males are blindness, seizures, and **diabetes mellitus**.

Mental impairment is severe with IQ ranging from 15 to 40.

Diagnosis

The diagnosis of Renpenning can tentatively be made on the basis of the clinical findings, including an analysis of the family history for evidence of X-linked inheritance. Linkage or segregation analysis using **DNA** markers in Xp11.4-p11.2 would be warrented to possibly rule out other X-linked mental retardation syndromes. Unfortunately, there are no laboratory or radiographic changes that are specific for Renpenning syndrome.

Sutherland Haan X-linked mental retardation syndrome also has microcephaly, short stature, small testes, and upslanting of the eye openings. Furthermore, this syndrome is localized from Xp11.3 to Xq12, which overlaps with the localization of Renpenning syndrome. However, males with Sutherland Haan also have spasticity, brachycephaly (disproportionate shortness of the head), and a thin appearance. It is possible these two syndromes have different mutations in the same gene.

The Chudley-Lowry syndrome, which also has microcephaly, short stature, and small testes, has yet to be localized. However, males have distinct facial features, similar to those observed in XLMR-hypotonic facies, and obesity. As this syndrome has not been mapped, it is possible that Chudley-Lowry syndrome results from a mutation in the same unknown gene responsible for Renpenning syndrome.

Three other X-linked mental retardation syndromes (Borjeson-Forssman-Lehman, X-linked hereditary bullous dystrophy, and XLMR-hypotonic facies) have microcephaly, short stature, and small testes. However, these conditions are located in different regions on the X chromosome and can be ruled out if DNA marker analysis is done in the family.

Treatment and management

As of early 2001, there is neither treatment nor cure for Renpenning syndrome. Early educational intervention may prove to be of some benefit for affected males. As some males have had seizures or diabetes mellitus, medication to control these conditions may be required at some point. Also some males may become blind. Some affected males may eventually have to live in facilities outside the home.

Prognosis

Life threatening or other health concerns have not been associated with Renpenning syndrome. However, the presence of severe mental impairment likely will result in some affected males living in a more controlled environment outside the home.

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Charles E. Schwartz, PhD

Retinitis pigmentosa

Definition

Retinitis pigmentosa (RP) refers to a group of inherited disorders that slowly leads to blindness due to abnormalities of the photoreceptors (primarily the rods) in the retina.

Description

The retina lines the interior surface of the back of the eye. The retina is made up of several layers. One layer contains two types of photoreceptor cells referred to as the rods and cones. The cones are responsible for sharp, central vision and color vision and are primarily located in a small area of the retina called the fovea. The area surrounding the fovea contains the rods, which are necessary for peripheral vision and night vision (scotopic vision). The number of rods increases in the periphery. The rod and cone photoreceptors convert light into electrical impulses and send the message to the brain via the optic nerve. Another layer of the retina, called the retinal pigmented epithelium (RPE), may also be affected.

KEY TERMS

Ophthalmoscope—An instrument, with special lighting, designed to view structures in the back of the eye.

In RP, the photoreceptors (primarily the rods) begin to deteriorate and lose their ability to function. Because the rods are primarily affected, it becomes harder to see in dim light, thus causing a loss of night vision. As the condition worsens, peripheral vision disappears, which results in tunnel vision. The ability to see color is eventually lost. In the late stages of the disease, there is only a small area of central vision remaining. Ultimately, this too is lost.

There are many forms of retinitis pigmentosa. Sometimes the disorder is classified by the age of onset or the **inheritance** pattern. RP can also accompany other conditions. This entry discusses "non-syndromic" RP, the type that is not associated with other organ or tissue dysfunction.

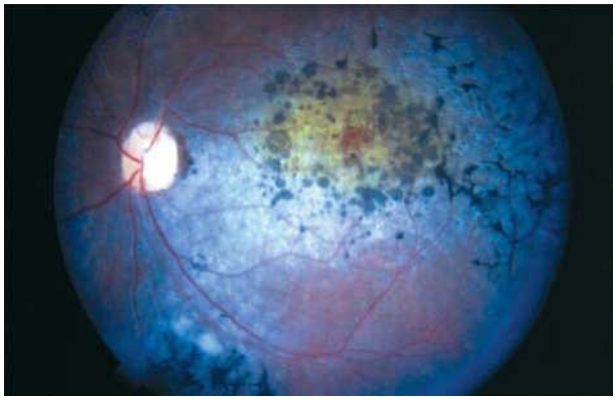
Genetic profile

Retinitis pigmentosa is an inherited disease that has many different modes of inheritance. RP, with any inheritance pattern, may be either familial (multiple family members affected) or isolated (only one affected person). In the non-sex-linked, or autosomal, form, it can either be a dominant or recessive trait. In the sex-linked form, called X-linked recessive, it is a recessive trait. This X-linked form is more severe than the autosomal forms. Two rare forms of RP are the digenic and mitochondrial forms.

Isolated RP cases represent 10–40% of all cases. Some of these cases may be the result of new gene mutations (changes in the genes). Other isolated cases are those in which the person has a relative with a mutation in the gene, but the relative is not affected by the condition.

Autosomal dominant RP (AdRP) occurs in about 15–25% of affected individuals. At least 12 different genes have been identified as causing AdRP. People with AdRP will usually have an affected parent. The risk for affected siblings or children is 50%.

Autosomal recessive RP (ArRP) occurs in about 5–20% of affected individuals. More than 16 genes have



A retinal photo showing retinis pigmentosa. *(Custom Medical Stock Photo, Inc.)*

been identified that cause this type of RP. In ArRP, each parent of the affected person is a carrier of an abnormal gene that causes RP. Neither of these carrier parents is affected. There is a two-thirds chance that an unaffected sibling is a carrier of RP. All of the children of an affected person would be a carrier of the ArRP gene.

Five to 15% of individuals with RP have X-linked recessive RP (XLRP). Six different genes have been identified as the cause of this type of RP. Usually in this type of inheritance, males are affected carriers, while females are unaffected carriers or have a milder form of the disease. The mother may be a carrier of the mutation on the X-chromosome. It is also possible that a new mutation can occur for the first time in an affected person. For families with one affected male, there is a mathematical formula called the Baysean analysis that can be applied to the family history. It takes into account the number of unaffected males to determine whether a female is likely to be a carrier or not. If a mother is a carrier, her children have a 50% chance of inheriting the RP gene. For affected males, all of their daughters will be carriers but none of their sons will be affected.

The digenic form of RP occurs when the affected person has inherited one copy of an altered ROM1 gene from one parent and one copy of an altered peripherin/RDS gene from the other parent. The parents are asymptomatic. Mitochondrial inheritance occurs when the **gene mutation** is in a mitochondrial gene. People with this type of RP have progressive hearing loss and mild myopathy. Both of these types of RP are very rare.

Demographics

The prevalence of RP is approximately 1 out of every 4,000 people in the United States and Europe. For other parts of the world, there are no published data. Nor is there any known ethnic difference in the occurrence of RP.

Signs and symptoms

The first symptoms, a loss of night vision followed by a loss of peripheral vision, usually begin in early adolescence or young adulthood. Occasionally, the loss of the ability to see color occurs before the loss of peripheral vision. Another possible symptom is seeing twinkling lights or small flashes of lights.

Diagnosis

When a person complains of a loss of night vision, a doctor will examine the interior of the eye with an ophthalmoscope to determine if there are changes in the retina. For people with advanced RP, the condition is characterized by the presence of clumps of black pigment in the inner retina (intraretinal). However, the appearance of the retina is not enough for an RP diagnosis since there are other disorders that may give the retina a similar appearance. There are also other reasons someone may have night blindness. Consequently, certain electrodiagnostic tests must be performed. An electroretinogram (ERG) determines the functional status of the photoreceptors by exposing the retina to light. The ERG uses a contact lens in the eye, and the output is measured on a special instrument called an oscilloscope. The functional assessments of visual fields, visual acuity, or color vision may also be performed.

The diagnosis of RP can be established when the following criteria are met:

- rod dysfunction measured by dark adaptation test or ERG
- progressive loss in photoreceptor function
- loss of peripheral (side) vision
- both eyes affected (bilaterality)

Molecular **genetic testing** is available on a research basis. Prenatal diagnosis for this condition has not yet been achieved.

Treatment and management

There are no medications or surgery to treat RP. Some doctors believe vitamins A and E will slightly slow the progression of the disease in some people. However, large doses of certain vitamins may be toxic and affected individuals should speak to their doctors before taking supplements.

If a person with RP must be exposed to bright sunlight, some doctors recommend wearing dark sunglasses to reduce the effect on the retina. Affected people should talk to their eye doctors about the correct lenses to wear outdoors.

Because there is no cure for RP, the affected person should be monitored for visual function and counseled about low-vision aids (for example, field-expansion devices). **Genetic counseling** is also appropriate. A three-generation family history with attention to other relatives with possible RP can help to clarify the inheritance pattern. For some people however, the inheritance pattern cannot be discerned.

Prognosis

There is no known cure for RP, which will eventually lead to blindness. The more severe forms will lead to blindness sooner than milder forms.

Resources

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American Association of the Deaf-Blind. 814 Thayer Ave., Suite 302, Silver Spring, MD 20910. (301) 588-6545.

American Optometric Association. 243 North Lindbergh Blvd., St. Louis, MO 63141. (314) 991-4100. <http://www.aoanet.org>.

Foundation Fighting Blindness Executive Plaza 1, Suite 800, 11350 McCormick Rd., Hunt Valley, MD 21031. (888) 394-3937. <http://www.blindness.org>.

National Retinitis Pigmentosa Foundation. 11350 McCormick Rd., Executive Plaza 1, Suite 800, Hung Valley, MD 21031-1014. (800) 683-5555. <http://www.blindness.org>.

Prevent Blindness America. 500 East Remington Rd., Schaumburg, IL 60173. (800) 331-2020. <http://www.prevent-blindness.org>.

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Amy Vance, MS
Dorothy Elinor Stonely

Retinoblastoma

Definition

Retinoblastoma is a **cancer** affecting one or both eyes. It occurs mainly in children under the age of four. Its name is derived from the area of the eye that is affected, the retina. The retina is the part of the eye that captures the images of the outside world and transfers these images to the brain. If the eye is thought of as a camera, the retina can be thought of as the film in the camera.

Description

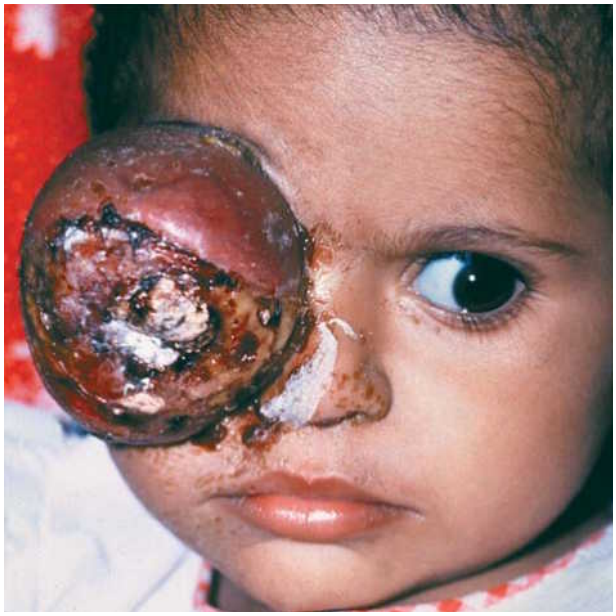
Retinoblastoma is the most common primary eye tumor of infancy and childhood, accounting for about one percent of all pediatric tumors. In about 75% of cases, retinoblastoma only affects one eye; when this occurs, it is referred to as unilateral retinoblastoma. In 25% of cases, it affects both eyes, and is referred to as bilateral retinoblastoma. Approximately 90% of children who present with retinoblastoma have no previous family history of the disease. However, in about 10% of cases, there is a definite family history of retinoblastoma.

Many of the early symptoms of retinoblastoma, such as intermittent pain of the eye, inflammation of the eye, and poor vision, are often overlooked. It is often a parent who notices the most visible sign of retinoblastoma, that being a whitish appearing pupil, known as leukocoria. If retinoblastoma is detected early enough, treatment such as surgery or radiation can result in a 95% cure and survival rate.

Genetic profile

The are two main types of retinoblastoma, called hereditary and nonhereditary. The vast majority of cases, approximately 90%, are nonhereditary, meaning that the children who develop retinoblastoma are the first ones in their family to have cancer of the eye. Ten percent of the cases are hereditary, meaning that someone in the immediate family, usually a parent, grandparent, aunt, uncle, brother or sister, also has the condition. In hereditary retinoblastoma, both eyes are usually affected. In nonhereditary retinoblastoma, usually only one eye is affected.

In 1986, after years of research, it was found that an abnormal **gene** on chromosome 13 is responsible for retinoblastoma. Part of chromosome 13 is responsible for normal growth and cellular division in the retina; in



Child with a large tumor proturuding from the right eye socket. *(Custom Medical Stock Photo, Inc.)*

retinoblastoma, this growth and division is uncontrolled, leading to cancer of one or both eyes.

In 40% of children who present with retinoblastoma, there will be an abnormality of chromosome 13 in every cell in that child's body, including the affected eye(s). In 60% of the children who have retinoblastoma, the abnormal chromosome will only be found in the eye.

As stated earlier, retinoblastoma can occur spontaneously (nonhereditary) or be seen in families (hereditary). If neither parent had retinoblastoma, then the chances of having a child with retinoblastoma is approximately one in 20,000. However, parents with a child having the condition should have a detailed retinal exam to see if they perhaps had retinoblastoma and were not aware of it. One percent of the time, this exam will reveal that one of the parents had a limited form of retinoblastoma that was never diagnosed. In this case, a full 45% of the parent's children will have the chance of developing retinoblastoma. In even rarer cases, the parent could have the gene for retinoblastoma without any evidence of the disease in their eyes. This is called a carrier state, and again, 45% of the parent's children will have the chance of developing retinoblastoma. There are now genetic tests to determine if a parent is a carrier of the condition. However, the current test is only 80% accurate, and costs between $2,500.00 and $4,000.00.

In hereditary retinoblastoma, if a parent has bilateral (seen in both eyes) retinoblastoma and decides to have children, then with each pregnancy, there is a 45% chance his or her children will develop retinoblastoma. Many of these children will also have tumors spread from their retinas into their brains at the time of birth. Other children will not develop tumors until they are two to three years of age. Most children born to a parent with bilateral retinoblastoma will also have the condition in both eyes. Fifteen percent of these children will have retinoblastoma in only one eye.

There is also hereditary retinoblastoma in which the parent has unilateral (in one eye) retinoblastoma. In this case, 7–15% of the children of these parents will develop retinoblastoma. Like the children born to a parent with bilateral retinoblastoma, most of the children (approximately 85%) born to parents with unilateral retinoblastoma will have bilateral retinoblastoma.

Demographics

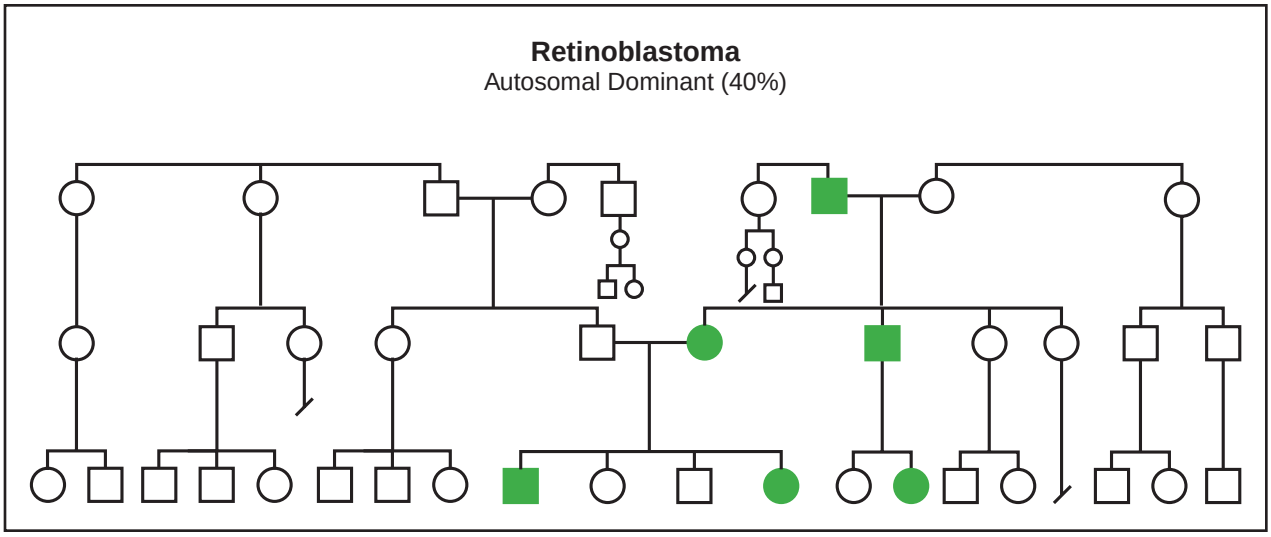
Retinoblastoma is the most common type of eye cancer in children. It occurs in approximately one in 20,000 births, which means that each year about 200–300 children are affected in the United States. The incidence of retinoblastoma in other areas of the world is thought to be approximately the same. As more and more children survive this condition and grow into adulthood and have their own families, the frequency of the condition in the population will probably increase. Retinoblastoma affects children of all races and is seen equally in both boys and girls.

Signs and symptoms

Since the successful management of retinoblastoma depends on detecting it early, the recognition of the signs and symptoms of the condition is critical. This is especially true for primary care physicians, who are often the first medical personnel to see infants or children with retinoblastoma.

There are many ways that retinoblastoma can present itself in infants and children. More than half of all patients with the condition will have a white pupil reflex, called leukocoria. In healthy infants and children, their pupils will appear black, or, when photographed, red. However, patients with retinoblastoma will often have a pupil that appears gray or white.

The second most common presenting sign of retinoblastoma, occurring about 25% of the time, is a crossed eye, a medical condition referred to as strabismus. The child's eye may appear to be looking out towards the ear, called *exotropia*, or inward towards the nose, called *esotropia*. It should be noted that three to four percent of all American children present with some form of strabismus, but not all of these children have



(Gale Group)

retinoblastoma. However, since 25% of children with retinoblastoma have strabismus, any child with this condition should have a detailed eye exam to rule out retinoblastoma.

While leukocoria and strabismus are the two most common presenting signs of retinoblastoma, there are other ways the condition may present itself. Other symptoms may include a red, painful eye, poor vision, orbital cellultis (inflammation of the skin and tissue around the eye), and amblyopia, or "lazy eye." Heterochromia, which is different colored irises (the colored part in the center of the eye surrounding the pupil), may also be the first signs of retinoblastoma.

Diagnosis

The diagnosis of retinoblastoma is frequently made by the parents of an infant or child with the condition. Often, the parents will tell the physician that they have noticed that their child's eye looks "white," or that the child's eye or eyes seem to drift to one side or the other.

When a child is born into a family that has a history of retinoblastoma, diagnosis of the condition can often be made before the baby leaves the hospital by an eye specialist, or ophthalmologist. If there is no family history, and the initial diagnosis is made by the parents or family physician, then the child can be sent to an ophthalmologist for a more thorough eye exam.

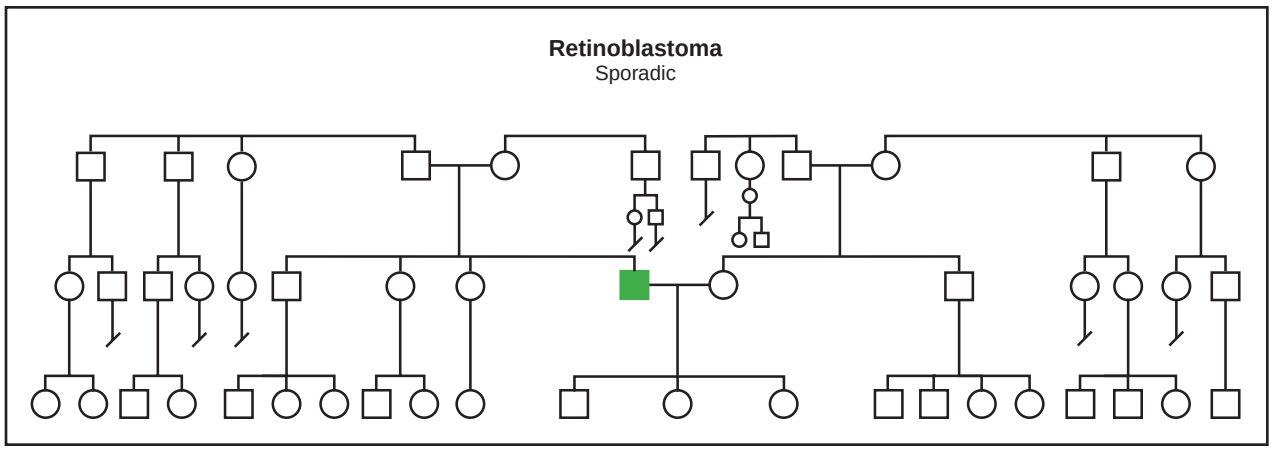
To examine a child for retinoblastoma, dilating drops are placed in both eyes to dilate (enlarge) the pupils and allow the ophthalmologist to view the retina. If a tumor is seen or suspected, an ultrasound examination, which uses sound waves to penetrate and outline structures in the eye, is used to confirm the presence of a tumor. A specialized x ray, called a CAT scan, which uses computers to take very detailed pictures of the inside of the body, can be used to see if there are tumors in other parts of the body.

Treatment and management

Treatment options for retinoblastoma have significantly increased over the past twenty years. The earliest form of treatment for retinoblastoma was *enucleation*, the removal of the major portion of the affected eye. This led to total loss of vision in that eye. While enucleation is still used, especially when the tumor is very large, newer, more sophisticated treatments have emerged that offer the chance to save at least some vision in the affected eye.

Lasers can be used in a treatment known as photocoagulation. This treatment is best used when the tumor is small and confined to the retina. The laser is actually used to burn and destroy blood vessels that feed the tumor, rather then directly on the tumor itself. The treatment can be repeated one or two times, and in some studies complete remission of the retinoblastoma was achieved in 70% of patients.

Another modality that works well with tumors that are confined to the retina is cryotherapy. It may be used as either the primary mode of treatment or in conjunction with other treatment modalities. Like photocogulation, cryotherapy has its highest success rates with smaller tumors. Unlike photocoagulation, cryotherapy uses extreme cold to destroy the tumor itself.



Pedigree analysis showing sporatic occurance of retinoblatoma within a family. *(Gale Group)*

Thermotherapy uses heat generated from ultrasound or microwaves to destroy the retinoblastoma tumor. While thermotherapy works well on its own with small tumors, it is even more effective when used with chemotherapy or radiation therapy, which are thought to make the tumor more susceptible to the heat generated by thermotherapy.

The use of conventional external beam radiation is still used for retinoblastoma, especially for tumors that are larger and have spread outside the retina. While radiation is applied directly to the tumor, with careful application the eye itself can be saved from destruction in about 75% of patients. In 35% of patients who receive external beam radiation, there is an increased risk for a retinoblastoma tumor to develop in the other eye within a 30-year time frame. Therefore, external beam radiation is generally only used when other conservative measures, such as cryotherapy or photocoagulation fail or cannot be used due to large tumor size.

Probably the most significant advancement in the treatment and management of retinoblastoma has come about in the use of chemotherapy. While in the past chemotherapy was only used to treat patients whose tumors had spread outside the eye, newer chemotherapy agents such as carboplatin and etoposide, along with older agents such as vincristine, are being used to treat tumors that are confined to the eye with significant success. Using these chemotherapeautic agents, it has been shown that tumors typically decrease in size 30–45%. This then allows more conservative and eye-sparing therapy such as cryotherapy and photocoagulation to be used much more effectively.

Prognosis

The prognosis for the vast majority of patients with retinoblastoma is excellent. In the United States, over 95% of children with retinoblastoma survive and lead healthy, productive lives.

Children who have unilateral retinoblastoma have at least one normal eye and can lead normal childhood lives, and even drive cars as they get older. The majority of children with bilateral retinoblastoma retain some vision in one eye, and sometimes both eyes. However, all children affected with bilateral retinoblastoma and 15% of children with familial unilateral retinoblastoma have a higher risk of developing other cancers throughout their lives. Therefore, children in these categories need to have regular medical checkups throughout their lives to watch for any signs of secondary cancers in areas such as bone, muscle, skin, and brain.

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Eye Cancer Network. 115 East 61st St., New York, NY 10021. (212) 832-8170. <http://www.eyecancer.com>.

National Eye Institute. Bldg. 31 Rm 6A32, 31 Center Dr., MSC 2510, Bethesda, MD 20892-2510. (301) 496-5248. 2020@nei.nih.gov. <http://www.nei.nih.gov>.

National Retinoblastoma Research and Support Foundation. PO Box 016880, 900 NW 17th St., Room 257, Miami, FL 33101-6880. (800) 226-2734.

University of Pennsylvania Cancer Center. 3400 Spruce St., Philadelphia, PN 19104. (215) 662-4000. <www.oncolink.upenn.edu>.

Edward R. Rosick, DO, MPH, MS

Retinoic acid embryopathy *see* **Accutane embryopathy**

Rett syndrome

Definition

Rett syndrome is a progressive neurological disorder seen almost exclusively in females. The most common symptoms include decreased speech, mental retardation, severe lack of coordination, small head size, and unusual hand movements.

Description

Dr. Andreas Rett first reported females with the symptoms of Rett syndrome in 1966. Females with this X-linked dominant genetic condition are healthy and of average size at birth. During infancy, head growth is abnormally slow and microcephaly (small head size) develops. Babies with Rett syndrome initially have normal development. At approximately one year of age, development slows and eventually stops. Patients with Rett syndrome develop autistic features. Involuntary hand movements are a classic feature of Rett syndrome.

Females with Rett syndrome may also develop seizures, curvature of the spine (**scoliosis**), irregular breathing patterns, swallowing problems, constipation, and difficulties walking. Some females with Rett syndrome are unable to walk. There is currently no cure for Rett syndrome. Most girls with Rett syndrome live until adulthood. The **gene** responsible for Rett syndrome has been identified and **genetic testing** is available.

Genetic profile

Rett syndrome is an X-linked condition. This means that the mutation (genetic change) responsible for Rett syndrome affects a gene located on the X chromosome.

KEY TERMS

Apraxia—Impairment of the ability to make purposeful movements, but not paralysis or loss of sensation.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Autism—A syndrome characterized by a lack of responsiveness to other people or outside stimulus. Often in conjunction with a severe impairment of verbal and non-verbal communication skills.

Microcephaly—An abnormally small head.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Neuron—The fundamental nerve cell that conducts impulses across the cell membrane.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

The affected gene is the methyl CpG-binding protein 2 (MECP2) gene. This gene makes a protein that regulates other genes. When there is a mutation in MECP2, the protein it makes does not work properly. This is thought to prevent normal neuron (nerve cell) development.

Rett syndrome is considered to be X-linked dominant in nature. Males have one X chromosome and one Y chromosome. Females have two X **chromosomes**. Males with a mutation in their MECP2 gene typically die as infants or are miscarried before birth. Rett syndrome is usually considered fatal in males because the Y chromosome cannot compensate for the MECP2 mutation on the X chromosome. Females with a mutation in the MECP2 gene develop Rett syndrome, but the presence of the second X chromosome in females carrying a normal MECP2 gene enables them to survive.

The severity of the syndrome in females is related to the type of mutation in the MECP2 gene and the activity of the X chromosomes. Normally, both X chromosomes have the same activity. However, the activity can be unequal. If the X chromosome with the mutation in the MECP2 gene is more active than the X chromosome without the mutation, the female is more severely

affected. The reverse is also true. If the X chromosome without the mutation is more active than the X chromosome with the mutation, the female is less severely affected.

If a woman has a mutation in her MECP2 gene, she has a 50% risk with any pregnancy to pass on her X chromosome with the mutation. However, it is uncommon for women with Rett syndrome to have children due to the severity of the disorder.

Demographics

The incidence of Rett syndrome is thought to be between 1 in 10,000 and 1 in 20,000 live births. It is seen almost exclusively in females. The vast majority of cases of Rett syndrome are sporadic in nature. Therefore, the risk of a family having more than one affected daughter is typically very low.

Signs and symptoms

Infants with Rett syndrome typically have normal size at birth. They develop normally until approximately 6–18 months of age. Development then slows, eventually stops, and soon regresses. Affected individuals are unable to do things they were once able to do. Girls with Rett syndrome lose the ability to speak, become uninterested in interacting with others, and stop voluntarily using their hands. The loss of language and eye contact causes girls with Rett syndrome to appear to be autistic. Between one and three years of age, girls with Rett syndrome develop the unusual hand movements that are associated with the disease. Patients wring their hands, clap their hands, and put their hands in their mouth involuntarily. Some patients with Rett syndrome also lose the ability to walk. If the ability to walk is maintained, the gait is very ataxic (uncoordinated, clumsy).

By preschool age the developmental deterioration of girls with Rett syndrome stops, but they continue to have lack of speech, inability to understand language, poor eye contact, mental retardation, ataxia, and apraxia (inability to make purposeful movements). Other common symptoms associated with Rett syndrome include seizures, constipation, irregular breathing, scoliosis, swallowing problems, teeth grinding, sleep disturbances, and poor circulation. As patients with Rett syndrome get older, their ability to move decreases and spasticity (rigidity of muscles) increases.

Diagnosis

The diagnosis of Rett syndrome is made when the majority of the symptoms associated with the disease are present. If a physician suspects an individual has Rett syndrome, DNA testing is recommended. Approximately 75% of patients with Rett syndrome have a mutation in the MECP2 gene. DNA testing can be performed on a blood sample, or other types of tissue from the body. If a mutation is found in the MECP2 gene, the diagnosis of Rett syndrome is confirmed.

Treatment and management

As of 2001, there is not a cure for Rett syndrome. Treatment of patients with Rett syndrome focuses on the symptoms present. Treatment may include medications that inhibit seizures, reduce spasticity, and prevent sleep disturbances. Nutrition is monitored in females with Rett syndrome due to their small stature and the constipation associated with the disorder.

Prognosis

In the absence of severe medical problems, most patients with Rett syndrome live into adulthood.

Resources

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International Rett Syndrome Association. 9121 Piscataway Rd., Clinton, MD 20735. (800) 818-RETT. <http://www.rettsyndrome.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Holly A. Ishmael, MS, CGC

RFH1 *see* **Renal failure due to hypertension**

Rhizomelic chondrodysplasia punctata

Definition

Rhizomelic chondrodysplasia punctata is a rare, severe, inherited disease. The main features are limb shortening, bone and cartilage abnormalities visible on x ray, abnormal facial appearance, severe mental retardation, profound psychomotor retardation, and cataracts. Skeletal abnormalities can be seen prenatally. Most affected persons die in infancy. No treatments are available.

Description

Rhizomelic chondrodysplasia punctata (RCDP) is caused by an abnormal protein in a part of the cell called the peroxisome. The inside of the cell contains compartments (called "organelles") that perform specific functions. The peroxisome functions in many metabolic processes, especially those involving lipids (fats) and hydrogen peroxide. Multiple peroxisomes are in almost every human cell. RCDP is one of many peroxisomal disorders, as well as a metabolic disorder.

Three other conditions are also called "chondrodysplasia punctata." These conditions are different from RCDP. They have almost the same name because it describes a feature that is present in all four conditions. However, the causes, features, and patterns of **inheritance** of the other chondrodysplasia punctata conditions are different from those of RCDP.

Genetic profile

Rhizomelic chondrodysplasia punctata is an autosomal recessive condition. This means that it occurs in both males and females, and often affects people who have no family history of the condition. Humans have two copies of every **gene**, one maternally and one paternally inherited. Autosomal recessive conditions occur when a person has two abnormal copies of the same gene. People who have one abnormal copy and one normal copy of a particular gene are unaffected; they are called "carriers." An affected person has inherited two abnormal RCDP genes, one from each carrier parent. The risk for the carrier parents to have another affected child is then 25% with each pregnancy.

In 1997, the gene that causes RCDP was identified. The gene is called PEX7 and it is on chromosome 6. Fifteen genes involved in the synthesis of peroxisomes have been identified in humans. These genes are called PEX genes, and the proteins they code for are called peroxins. Disorders caused by abnormalities of peroxin proteins are often called "peroxisomal biogenesis" disorders.

The PEX7 gene codes for a peroxisomal component that helps transport other important proteins into the peroxisome. The proteins to be transported contain a signal, called "PTS2" (peroxisome targeting sequence 2) that is recognized by the receptor on the peroxisome. When PEX7 is abnormal, the receptor that usually recognizes and helps transport the PTS2 proteins is abnormal. Thus, the abnormality of this one receptor has a cascade effect on many other proteins.

Demographics

Rhizomelic chondrodysplasia punctata is quite rare. It occurs in fewer than 1/100,000 births. The incidence of peroxisomal biogenesis disorders is approximately 1/50,000 births; RCDP accounts for fewer than one fifth of these.

Signs and symptoms

"Rhizomelic" refers to shortening of the bones near the center of the body (the bones of the thighs and upper arms more so than the bones of the forearms and lower legs). "Chondro" refers to cartilage and "dysplasia" to abnormal development. "Punctata" refers to specific abnormalities seen on radiological studies such as x ray. The ends of the bones near joints appear to be spotted. The spots represent dense, abnormal cartilage. The spots are also called "punctate calcifications." Other abnormalities include frozen joints (called contractures), abnormal facial features, cataracts, hearing loss, severe mental retardation, and profound psychomotor retardation. People with RCDP may also have other bone abnormalities, small heads, coarse and sparse hair, and dry, red skin.

The proximal shortening of the bones causes short stature, which is apparent before birth. Growth after birth is retarded as well. The rhizomelic shortening is severe, and occurs to the same degree on both sides of the body. The stippling (spotting) of the bones mainly involves the ends of the bones near the hip, knee, elbow, and shoulder. "Severe" mental retardation describes cognitive deficits worse than those of typical **Down syndrome**. Some researchers have described degeneration of brain tissue after birth. Researchers are not sure of the reason for this; it may be due to toxic effects of excess phytanic acid. Cataracts are symmetrical and occur in both eyes. The abnormal facial features have been called "koala bear facies." Facial features include a broad forehead and a saddle nose.

A subset of people with RCDP do not have some of the typical symptoms, such as shortening of proximal bones and/or severe mental retardation. The diagnosis in these individuals was confirmed to be RCDP. Therefore, the spectrum of features in RCDP is variable;

KEY TERMS

Anticoagulant—Drugs used to prevent blood clots.

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Differentiate—Specialized development to perform a particular function.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Plasmalogens—Fat molecules that are important components of cells and of the myelin sheath that protects nerve cells.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Psychomotor—Movement produced by action of the mind or will.

some people are much more mildly affected than is typical. These differences in severity appear to be associated with different mutations in the PEX7 gene.

Diagnosis

Although suspicion of RCDP is raised by the physical and radiographic features, the diagnosis is made by laboratory testing. People with RCDP have very specific biochemical abnormalities, i.e. abnormal levels of particular substances in bodily fluids. These abnormalities are due to the underlying defect in the peroxisome. The specific abnormalities are: 1) deficient plasmalogen synthesis with very low plasmalogen levels in red blood cells, 2) inability to process (oxidize) phytanic acid leading to elevated levels of phytanic acid in the blood, and 3) an unprocessed form of peroxisomal thiolase. Phytanic acid levels are normal at birth and increase to at least ten times normal by one year of age. Some experts recommend that confimatory studies be performed on cells obtained by skin biopsy.

The biochemical studies diagnostic of RCDP can be performed prenatally on cells obtained by chorionic villus sampling (CVS) or **amniocentesis**. CVS is usually performed at 10–12 weeks of pregnancy and amniocentesis is usually performed after 15 weeks of pregnancy. RCPD may be suspected in a fetus based on ultrasound findings.

Each feature of RCDP is seen in many other conditions, for example rhizomelic limb shortening is seen in other conditions that cause dwarfism. Chondrodysplasia punctata is seen in many inherited conditions but can also be caused by prenatal exposure to the anticoagulant drug, Warfarin. Doctors who specialize in diagnosing rare genetic conditions use subtle differences between the symptoms of these conditions to narrow their search for the suspected diagnosis. Many peroxisomal disorders have abnormal very long chain fatty acids (VLCFAs); VLCFA levels are normal in RCDP.

Two rare conditions cannot be distinguished from RCDP by physical symptoms. These conditions involve specific abnormalities of plasmalogen synthesis. RCDP is caused by abnormal peroxisome synthesis, which leads to multiple biochemical abnormalities including deficient plasmalogen synthesis. In contrast, these two conditions each affect only one protein. The proteins affected are dihydroxyacetone phosphate acyltransferase (DHAPAT) and alkyl dihydroxyacetone phosphate synthase. People with deficiencies in these two proteins have normal thiolase and normal phytanic acid levels.

RCDP is the only condition known to be caused by abnormal PEX7 gene. **Genetic testing** is another method to confirm the diagnosis. A doctor who specializes in medical genetics can determine whether this testing is available clinically.

Treatment and management

The only treatments for RCDP are supportive therapies to treat symptoms. People with RCDP, especially those who are less severely affected, benefit from symptomatic support of various specialties such as ophthalmology and physical therapy. Dietary restrictions or supplements have shown promise in the treatment of some peroxisomal disorders. The enormous obstacle in the severe conditions is that many of the abnormalities develop before birth and are irreversible. The multiple biochemical abnormalities of RCDP also complicate treatment efforts. Some researchers have tried to improve the function of the deficient metabolic process. This treatment, if it works, will probably benefit mildly affected patients more than the typically severely affected person with RCDP.

The underlying cause of the severe mental retardation is not well understood. Some abnormalities of nerve tissue have been described. In many peroxisomal disor-

ders similar to RCDP the nerve tissue migrates abnormally before birth. This abnormal migration is not present in RCDP. It appears that in RCDP the nerve tissue does not differentiate properly once it has migrated to the correct location in the body.

Prognosis

The prognosis for the typical individual with RCDP, who is severely affected, is death in infancy. Most affected infants die in the first two years of life. However, exceptions have reported in the medical literature. Individuals who lived past the age of 10 years have been reported. For atypical, mildly affected patients, prognosis is variable.

Scientists' understanding of peroxisomal disorders, and of the peroxisome itself, increased enormously in the last five years. Developing effective treatments of RCDP is a great challenge. But having a better understanding of the underlying cause is the first step. This has also increased awareness of RCDP, probably leading to more accurate diagnoses and higher clinical suspicion. A correct diagnosis is critical in providing accurate recurrence, prognosis, and prenatal diagnosis information.

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International Patient Advocacy Association. 800 Bellevue Way NE, Suite 400, Bellvue, WA 98004. (425) 462-4037 or (310) 229-5750 or (800) 944-7823 x4037. lvp.ipaa@att.net. <http://www.vanpelt-ipaa.com>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Rhizomelic Chondrodysplasia Punctata (RCP) Family Support Group. 137 25th Ave., Monroe, WI 53566.

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Michelle Queneau Bosworth, MS, CGC

Rhodopsin

Definition

Rhodopsin is the visual pigment that "senses" light in the rod cells of the retina.

Where is rhodopsin?

Rhodopsin is found at the back of the eye, in the retina. The retina is the area of the eye that senses light, interprets that information, and transmits it to the brain for further interpretation. Two types of light-sensing cells are found in the retina: rods and cones. In a simplified explanation, rod cells are responsible for black and white vision, whereas cone cells are responsible for color vision. This is true as far as it goes, but there are many more differences between rods and cones.

In rod cells, rhodopsin is responsible for phototransduction, the process of turning light into chemical and electrical energy. Rhodopsin is responsible for phototransduction in rod cells, but not in cone cells. Three different proteins, similar to rhodopsin, govern phototransduction in the cone cells. Each of these three phototransducers responds to a different color of light, which allows persons with normal color vision to see the entire color spectrum.

In order to understand more of the structure, function, and location of rhodopsin, a discussion of cells and cell membranes is necessary. Every human cell has a cell membrane that separates the environment inside the cell (intracellular environment) from the extracellular (outside the cell) environment. Cell membranes are made up of lipids, which are hydrophobic substances. Hydrophobic literally means "fear of water." Oil is an example of a hydrophobic substance. If oil is added to water, the oil will separate itself from the water. Basically, the lipids in the cell membrane form a similar water-excluding ball, but the inside of the ball will contain water (and other intracellular fluids). Each rhodopsin molecule crosses the cell membrane seven times, and each area of the protein in the cell membrane is called a transmembrane domain. These transmembrane domains (which are hydrophobic) dictate an interesting structure for rhodopsin. Imagine folding a hose seven times to hold it in your hand. The structure for rhodopsin is at least that complex. One reason to mention that rhodopsin has the seven transmembrane domains is because that structure is common to G proteins, and rhodopsin is a G protein. G proteins are generally involved in a biological cascade. A biological cascade is a system where a small initial input (like a brief flash of light) can result in a rather large output.

How does rhodopsin turn light into a chemical signal?

Rhodopsin is a combination of two different molecules, retinal and opsin. Retinal is a derivative of vitamin A, and opsin is a protein. When rhodopsin is not activated, retinal is in the 11-cis configuration. When light hits 11-cis retinal, it changes its shape to become all-trans retinal. This is the only light-sensitive step in vision (in the rod cells). What the configurations are called, and what those names mean is not as important as the fact that this light-dependent change in conformation results in light being converted into chemical energy.

Once retinal reaches the all-trans conformation, opsin also changes its shape. The new opsin-retinal complex is called metarhodopsin II. Metarhodopsin II is a semistable complex that is the active form of rhodopsin. Metarhodopsin II, unlike the inactive rhodopsin, is able to bind a protein called transducin. Each metarhodopsin II can bind to many transducins (literally hundreds). These transducins then cause a decrease in cGMP concentration, and one transducin molecule can cause the breakdown of more than 1,000 cGMP per second. One can clearly see why the G protein cascades are excellent systems for amplifying a signal.

Mutations in rhodopsin

Mutations in rhodopsin can result in two different disorders—**retinitis pigmentosa** and congenital stationary night blindness. Retinitis pigmentosa (RP) affects about one in 3,000 persons living in the United States, and about 1.5 million persons worldwide. Many mutations, not just mutations of the rhodopsin **gene**, lead to RP. The disorder may be inherited in an X-linked recessive fashion in 8% of all cases, an autosomal dominant fashion in 19% of cases, or as an autosomal recessive disorder in 19% of all cases. In the rest of the cases (54%), the mutations do not follow classical genetic patterns of **inheritance**. Mutations in rhodopsin have been found to cause approximately 20% of the autosomal dominant form of RP. The rhodopsin gene is located at the 3q locus of chromosome 3.

Patients with retinitis pigmentosa exhibit symptoms that include night blindness, abnormal pigment accumulation in the retina, and a progressive decrease in the visual fields. The patient's vision decreases from the outermost edges in. The age of onset of the disorder may be as young as six months, but most patients experience the first symptoms between ages 10 and 30. In RP, the patient's rod cells usually degenerate first, followed by a loss of cone cells.

Symptoms may often present after a motor vehicle accident. Not only is the age of onset variable, but the severity of the disease is as well. Patients with the same mutation, even within the same family, exhibit differing severities of the disorder. Mutations in rhodopsin may also cause autosomal recessive cases of RP.

Congenital stationary night blindness (CSNB) is another disorder that can be caused by mutations in the rhodopsin gene. Patients with CSNB, as may be deduced from the name, experience night blindness. However, unlike RP, patients with CSNB do not experience degeneration (death) of cells of the retina (rod and cone cells). Patients with CSNB are thought to have an overactive transducin molecule, which prevents their rods from functioning normally. A mutation in transducin, which also causes CSNB, supports this theory, since this transducin is also thought to be overly active.

Treatment

As of 2001, no effective treamtment for RP exists. However, new treatments are being explored for RP. Experiments in rats have shown that rod cells can be affected by **gene therapy**. Although gene therapy has not been successfully demonstrated as of this printing, at least the hope now exists that eventually gene therapy may be applied to the problem of RP. Previously, addition of a new gene into a non-dividing cell line had been thought to be technically insurmountable. Another experiment in rodents offers hope for those who have autosomal recessive RP. In rats with autosomal recessive RP, retinal pigment transplantation has successfully treated them according to Columbia University's Retinal Transplant newsletter. This technique might prove promising in humans.

Prognosis

The prognosis for persons with RP is extremely variable. Persons with CSNB will experience night blindness throughout their lives.

Resources

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Michael V. Zuck, PhD

Rhodopsin related retinitis pigmentosa *see* **Rhodopsin**

Rhymes syndrome *see* **Retinitis pigmentosa**

Ribonucleic acid *see* **RNA**

RIEG *see* **Rieger syndrome**

Rieger syndrome

Definition

Rieger syndrome is a rare disorder characterized by absence and/or malformation of certain teeth, mild craniofacial (relating to the head and the face) abnormalities, and various eye abnormalities. The eye abnormalities, referred to as Rieger eye malformations, may be present separately or as a part of Rieger syndrome.

Description

First characterized by Herwigh Rieger, an Austrian ophthalmologist in 1935, Rieger syndrome is a dominantly inherited disease. Disease expression is highly variable, including craniofacial, ocular, and dental malformations. Symptoms may also include **myotonic dystrophy** (a condition characterized by delay in the ability to relax muscles), umbilical abnormalities (abnormalities relating to where the umbilical cord attaches to a baby), and other defects. Psychomotor retardation, a slowing of the motor action directly proceeding from mental activity, occurs in some cases.

Rieger syndrome is also sometimes referred to as goniodysgenesis hypodontia, iridogoniodysgenesis with somatic anomalies, or RGS. It is a multiple congenital anomaly syndrome, a syndrome marked by multiple abnormalities at birth. Currently, there are two genetic types of Rieger syndrome identified. Type I results from a mutation on chromosome 4 and Type II on chromosome 13.

Genetic profile

Rieger syndrome is inherited as an autosomal dominant disease. In autosomal dominant **inheritance**, a single abnormal **gene** on one of the autosomal **chromosomes** (one of the first 22 non-sex chromosomes) from either parent can cause the disease. One of the parents will have the disease (since it is dominant) and is the carrier. Only one parent needs to be a carrier in order for the child to inherit the disease. A child who has one parent with the disease has a 50% chance of also having the disease.

There is evidence that there is more than one genetic form of Rieger syndrome. The disease gene responsible for Rieger syndrome Type I is caused by mutations in the RIEG1 gene, which is located on the long arm (q) of chromosome 4 (4q25-Q26).

Linkage studies have indicated that a second type of Rieger syndrome, Type II, maps to the long arm of chromosome 13, at 13q14 (gene RIEG2).

Demographics

Rieger syndrome is very rare. Little is known in regard to the number of affected individuals or whether certain areas or ethnic groups are at a greater risk. Since the disease appears to be inherited in an autosomal dominant manner, meaning that it is transmitted on one of the non-sex chromosomes, males and females have an equal chance of acquiring the abnormal gene from their parents.

Signs and symptoms

The symptoms of Rieger syndrome are expressed variably. The main symptoms of Rieger syndrome are:

- Ocular malformations, called Rieger eye malformations, include underdeveloped iris, a small cornea (microcornea), an opaque ring around the outer edge of the cornea, adhesions (abnormal union of surfaces normally separate) in the front of the eye, and/or displacement of the pupil of the eye so that it is not centered.
- Dental abnormalities include a congenital condition causing a fewer number of teeth than normal (hypodontia); a condition in which a single tooth, pairs of teeth, or all the teeth are smaller than normal (microdontia), and/or cone-shaped.
- Craniofacial abnormalities include a protruding lower lip, a broad, flat bridge of the nose, and/or underdeveloped bones of the upper jaw (hypoplasia) causing the face to have a flat appearance.

Other conditions that have been found in some patients with Rieger syndrome are:

- Anal stenosis (a small anal opening).
- Failure of the skin around the navel to decrease in size after birth.
- Protrusion of intestine through a weakness in the abdominal wall around the navel (umbilical hernia).
- **Glaucoma** (increased pressure within the eyeball) may result from the ocular malformations associated with Rieger syndrome, including defects in the angle of the eye that is created by the iris and cornea (trabeculum),

KEY TERMS

Cornea—The transparent structure of the eye over the lens that is continous with the sclera in forming the outermost, protective, layer of the eye.

Craniofacial—Relating to or involving both the head and the face.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Microcornea—Abnormal smallness of the cornea.

Microdontia—Small teeth.

Myotonia—The inability to normally relax a muscle after contracting or tightening it.

Myotonic dystrophy—A form of muscular dystrophy, also known as Steinert's condition, characterized by delay in the ability to relax muscles after forceful contraction, wasting of muscles, as well as other abnormalities.

Ocular—A broad term that refers to structure and function of the eye.

Oligodonita—The absence of one or more teeth.

Psychomotor—Movement produced by action of the mind or will.

Stenosis—The constricting or narrowing of an opening or passageway.

the vein at the corner of the eye that drains the water in the eye into the bloodstream (schlemm), and the associated adhesions. Glaucoma can result in damage to the optic disk and gradual loss of vision, causing blindness in approximately 50% of affected individuals.

Additional conditions have sometimes occurred in conjunction with Rieger syndrome. Whether they are separate entities in which the Rieger eye malformations are present or part of Rieger syndrome is not determined. These conditions are:

- Myotonia (a condition in which the muscles do not relax after contracting).
- Myotonic dystrophy (a chronic progressive disease causing muscles to atrophy, slurred speech, failing vision, droopy eyelids, and general muscle weakness).
- Conductive deafness (hearing loss in which sound does not travel well to the inner ear).
- Less than average intellectual function associated with problems in learning and social behavior.

Diagnosis

This disorder can be detected soon after birth if the eye defects are visible. When the eye defects are not visible during the first month of life, Rieger syndrome is usually detected in early childhood when the eye and dental defects become apparent.

Molecular **genetic testing** for the RIEG1 and RIEG2 genes is not generally available. But since the molecular structure of the genes has been identified, the possibility now exists for DNA-based testing for diagnosis and **genetic counseling**.

Genetic counseling

Genetic counseling may be beneficial for patients and their families. Only one parent needs to be a carrier in order for the child to inherit the disease. A child has a 50% chance of having the disease if one parent is diagnosed with the disease and a 75% chance of having the disease if both parents have Rieger syndrome.

Prenatal testing

For couples known to be at risk for having a baby with Rieger syndrome, testing may be available to assist in prenatal diagnosis. Prior testing of family members is usually necessary for prenatal testing.

Either chorionic villus sampling (CVS) or **amniocentesis** may be performed for prenatal testing. CVS is a procedure to obtain a small sample of placental tissue, called chorionic villi tissue, for testing. Examination of fetal tissue can reveal information about the defects that leads Rieger syndrome. Chorionic villus sampling can be performed at 10–12 weeks gestation.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus and the amniotic sac, and withdrawing a small amount of amniotic fluid. **DNA** can be extracted from the fetal cells contained in the amniotic fluid and tested. Amniocentesis is performed at 16–18 weeks gestation.

Tissue showing the **gene mutation** for Rieger syndrome Type I or II obtained from CVS or in amniotic fluid is diagnostic.

Related disorders

A number of disorders are similar to Rieger syndrome. Comparisons may be useful for a differential diagnosis. These related disorders include:

- Cat-eye syndrome, a rare disorder marked by a cleft along the eyeball affecting the iris, the membrane that

covers the white of the eyeball (choroid), and/or the retina and causing a vertical pupil; abnormalities such as small polyps or pits near the front of the outer ear; and absence of the opening, duct, or canal of the anus. Other symptoms may include mild mental deficiency and heart defects.

- Ectodermal dysplasias, a group of hereditary syndromes affecting the skin, its derivatives, and some other organs. Symptoms include predisposition to respiratory infection, eczema, poorly functioning sweat glands, abnormal hair and nails, and difficulties with the nasal passages and ear canals.
- Eye, anterior segment dysgenesis, a rare congenital disorder resulting in abnormal tissue development of the outer eye segment. In less severe cases, the back of the outer surface of the cornea is nontransparent (embryotoxin). Symptoms include ocular abnormalities and malformations of the teeth, abdominal wall, skeleton, and heart.

It is generally thought that Axenfeld anomaly, marked by defects limited to the outer part of the field of vision of the eye, should not be considered a separate entity of Rieger syndrome.

Treatment and management

A physician familiar with the range of problems seen in individuals with Rieger syndrome is important for appropriate health supervision. Treatment should include assistance finding support resources for the family and the individual with Rieger syndrome.

Treatment of Rieger syndrome is focused on treating the symptoms expressed. Depending on what they are, these treatments may include:

- Drug therapy for glaucoma, usually a topical beta blocker in the form of eye drops. Laser surgery may be performed on those patients in whom the pressure in the eye is not relieved by medications.
- Prostheses (false teeth) or other orthodontic interventions for dental malformations.
- Other surgical management of congenital anomalies includes repair of an umbilical hernia that does not close by itself and plastic surgery for craniofacial abnormalities.

Prognosis

Prognosis depends upon the severity of the disease. Eye defects may lead to severly impaired vision or blindness. Rieger syndrome does not generally lead to a shortened life span.

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ORGANIZATIONS

Blind Children's Fund. 4740 Okemos Rd., Okemos, MI 48864-1637. (517) 347-1357. <http://www.blindchildrensfund.org>.

National Association for Parents of the Visually Impaired. PO Box 317, Watertown, MA 02472. (617) 972-7441 or (800) 562-6265. <http://www.spedex.com/napvi>.

National Association for Visually Handicapped. 22 West 21st Street, New York, NY 10010. (212) 889-3141. <http://www.navh.org>.

National Eye Institute. Bldg. 31 Rm 6A32, 31 Center Dr., MSC 2510, Bethesda, MD 20892-2510. (301) 496-5248. 2020@nei.nih.gov. <http://www.nei.nih.gov>.

National Foundation for Ectodermal Dysplasias. PO Box 114, 410 East Main St., Mascoutah, IL 62258-0114. (618) 566-2020. Fax: (618) 566-4718. <http://www.nfed.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Vision Community Services. 23 A Elm St., Watertown, MA 02472. (617) 926-4232 or (800) 852-3029. <http://www.mablind.org>.

OTHER

OMIM—Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?db=OMIM>

Rarelinks: A site for parents and caregivers dealing with Rieger syndrome. <http://rarelinks4parents.homestead.com/index.html>

Jennifer F. Wilson, MS

Riley-Day syndrome *see* **Familial dysautonomia**

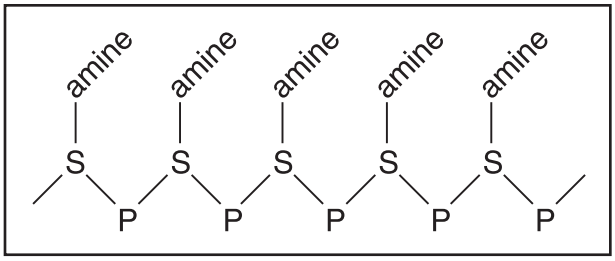
RNA (Ribonucleic acid)

Ribonucleic acid (RNA) conveys genetic information and catalyzes important biochemical reactions. Similar, but not identical, to a single strand of deoxyribonucleic acid (**DNA**), in some lower organisms, RNA replaces DNA as the genetic material. As with DNA, RNA follows specific base pairing rules, except that in RNA the base uracil replaces the base thymine (i.e., instead of an adenine-thymine or A-T pairing, there is an adenine-uracil or A-U pairing). Accordingly, when RNA acts as a carrier of genetic information, uracil replaces thymine in the genetic code.

In humans, messenger RNA (mRNA) is the product of transcription and acts to convey genetic information from the nucleus to the protein assembly complex at the ribosome. The ribsome is composed of ribosomal RNA (rRNA) and other proteins. Transfer RNAs (tRNA) act to catalyze the translation process by acting as carriers of specific amino acids. Because tRNAs bind to specific sites on the strand of mRNA, the sequence of amino acids subsequently inserted into the synthesized protein is both specific and genetically determined by the nucleotide sequence in DNA from which the mRNA strand was originally transcribed.

Other forms of RNA perform important roles in other biochemical reactions. Regardless of function, RNA is a biopolymer made up of ribonucleotide units and is present in all living cells and some viruses. The chemical units of RNA are ribonucleotide monomers consisting of a ribose sugar ($C_5H_{10}O_5$) phosphorylated at the third carbon (C3) and linked to one of four bases through a type of chemical linkage formed between a sugar and a base by a condensation reaction (glycosidic bond). The four bases found in RNA are adenine (A), guanine (G), cytosine (C), and uracil (U). Other bases may also be found, although they are generally modified versions of these four (e.g., methylated bases are found in parts of tRNA).

The single nucleotides (monomers) of RNA form a linear chain by linking their phosphate groups and sugars in phosphodiester bonds. RNA does not form a double stranded alpha-helix as does DNA. In some parts of the RNA molecule, there is folding into alpha-helical-like regions. Corresponding to their unique functions, messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA) all have different three-dimensional structures. In higher eukaryotic organisms, different RNAs are found distributed throughout the cell—in the nucleus, cytoplasm, and also in cytoplasmic organelles such as mitochondria and, in plants, chloroplasts.



The molecular structure of RNA. *(Gale Group)*

The nucleus is the chief site of RNA synthesis and the source of all cytoplasmic RNA, while mitochondria and chloroplasts synthesize their RNA from their own DNA. rRNA is synthesized by the nucleoli within the nucleus, while the high molecular weight precursor to cytoplasmic mRNA, sometimes termed heterogeneous nuclear or hnRNA, is transcribed on the DNA chromatin. Low molecular weight RNA also occurs in the nucleus and consists partly of tRNA and partly of RNA, which has a regulatory function in **gene** activation. The cytoplasm contains tRNA and rRNA in the ribosomes and mRNA in polysomes, or polyribosomes. The latter are the structural units of protein biosynthesis, consisting of several ribosomes attached to a strand of mRNA.

The function of mRNA is to transcribe the information held in DNA. In the cells of eukaryotic organisms, the first transcriptional product is the long, heterogenous nuclear RNA, or hnRNA. This contains both the nucleotide sequences eventually transcribed into polypeptides and large tracts of sequences not translated. Non-translated sequences are termed introns (or intervening sequences). Removal of introns, and other untranslated portions of the molecule, edits hnRNA into mRNA molecules. After editing removes as much as 90% of hnRNA, the resulting mRNA molecules are transported into the cytoplasm.

rRNA is located within ribosomes, the sites of protein biosynthesis. Ribosomes are large ellipsoid cytoplasmic organelles consisting of RNA and protein.

tRNA, the smallest known functional RNA, is essential for protein biosynthesis. Its purpose is to transfer a specific amino acid from the cytoplasm and incorporate it into the growing polypeptide chain on the polysome. Different tRNAs contain between 70 and 85 nucleotides. The most characteristic feature of tRNA is that it contains the anticodon, a sequence of three nucleotides specific for the mRNA codon sequence. There is at least one tRNA per cell bearing the anticodon for each of the 20 amino acids. The aminoacyl-tRNA (the tRNA carrying the amino acid) binds to the large subunit of a ribosome, where antiparallel basepairing occurs between the anti-

codon of the tRNA and the complementary codon of the associated mRNA. The specificity of this base pairing ensures that the amino acid inserts into the correct position in the growing protein polypeptide chain. During translation, the deacylated tRNA (i.e., with its amino acid removed) is released from the ribosome and becomes available once again for recharging with its amino acid.

DNA-dependent RNA synthesis is the process of RNA sythesis on a template of DNA. According to the rules of base pairing, the base sequence of DNA determines the synthesis of a complementary base sequence in RNA. Assisted (catalyzed) by the enzyme RNA polymerase, the growing RNA chain releases from the template so that the process can start again, even before the previous molecule is complete. Termination codons and a termination factor known as rho-factor end the synthesis process. In certain viruses, RNA-dependent RNA synthesis occurs, with the viral RNA acting as a template for the synthesis of new RNA.

Judyth Sassoon, ARCS, PhD

Roberts SC phocomelia

Definition

Roberts SC phocomelia is a rare genetic condition that causes severe abnormalities in arm and leg bones. Other abnormalities, such as mental retardation, may also be present.

Description

Roberts SC phocomelia was first described in the year 1919. In the past, Roberts SC phocomelia syndrome was described as two separate syndromes: Roberts syndrome, and SC or pseudo-thalidomide syndrome. More recent examination, however, indicated that they are the same disorder. The term "pseudo-thalidomide" was originally used to describe individuals with limb shortening, as the medication thalidomide is known to cause limb abnormalities in the babies of women taking it during pregnancy.

Phocomelia is a condition in which the hands and feet are present, but the arms and legs are absent. The hands and feet are attached directly to the body. Usually there is greater shortening in the arms than in the legs. People with Roberts SC phocomelia syndrome have varying degrees of hypomelia, which means that the limbs are not fully developed. Some are born without the upper bones of the arms or the legs. This is referred to as tetraphocomelia. Some people, though, have a less severe form of limb shortening.

In addition to the limb abnormalities, 80% of individuals with the syndrome have a small head (microcephaly). In addition, most people with the syndrome have some degree of mental retardation. Most also have facial problems affecting the development of the upper lip (cleft lip) and incomplete development of the palate (the roof of the mouth).

Genetic profile

Roberts SC phocomelia is inherited in an autosomal recessive fashion. This is a pattern in which the child receives one nonfunctioning (abnormal) **gene** from each parent. When a woman and man who both carry one abnormal gene for Roberts SC phocomelia have children, there is a 25% chance that they will each pass along the gene for the syndrome. People who are termed "carriers" are not affected by the disorder, as they have only one copy of the gene that causes Roberts SC phocomelia. The chances are 50% that they will have a child who is also a carrier of the disorder. The chances are 25% that they will have a baby who is neither a carrier nor affected with Roberts SC phocomelia.

The specific gene that causes the syndrome is not yet known, and there is no direct genetic test to identify a potential carrier of the disease.

In many of the individuals who have been diagnosed with Roberts SC phocomelia, a unique feature may be observed on some of their **chromosomes**. The exact association of this unusual observation with the syndrome is not yet understood.

Demographics

The exact number of people with the syndrome is not known, as some infants who die before or shortly after birth are never diagnosed or are diagnosed incorrectly. The syndrome affects males and females equally. There is no specific country or region of the world where the disorder is more common.

Signs and symptoms

In the bones of the lower arm (radius and ulna), limb shortening or absence of limbs is evident in approximately 97% of people with the syndrome. The upper arm (humerus) is affected 77% of the time. A missing or shortened thighbone (femur) occurs in about 65% of affected individuals. The bones in the lower leg (tibia and fibula) are shortened or absent in 77% of those with the disorder.

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid that surrounds a developing baby during pregnancy.

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Genetic test—Testing of chromosomes and genes from an individual or unborn baby for a genetic condition. Genetic testing can only be done if the gene is known.

Ultrasound evaluation—A procedure which examines the tissue and bone structures of an individual or a developing baby.

It is often very hard to flex or bend the knees, ankles, wrists, and/or elbows. While the feet and hands are almost always present, there may be fewer than normal fingers and toes, or shortened fingers. Sometimes the fingers are fused together (syndactyly).

People with the syndrome are smaller than other babies the same age, both before and after birth. Babies with Roberts SC phocomelia syndrome may have thin hair that is often described as silvery in color. In addition, most people with Roberts SC phocomelia syndrome are born with a cleft lip (a failure of the upper lip to close completely) and cleft palate (an opening in the roof of the mouth). Other abnormalities that may occur include a small and underdeveloped chin, a short neck, heart and kidney problems, prominent and widely spaced eyes, and unusually shaped ears.

Diagnosis

This disorder has been diagnosed during pregnancy at 12 weeks, through a test called an ultrasound evaluation. In these incidences, developmental problems with the growth and formation of both the arms and legs were noted. Sometimes the syndrome cannot be diagnosed by ultrasound until later in the pregnancy, when the limb shortening or absence becomes more obvious, and sometimes it cannot be diagnosed by ultrasound at all. Other abnormalities that might be seen by ultrasound include cleft lip, increased distance between the eye sockets, and extra fluid in some of the structures of the brain (**hydrocephalus**). Excess amniotic fluid levels, kidney problems, and an opening in the spine (**spina bifida**) have also been found. However, an exact diagnosis of the syndrome cannot be made by ultrasound evaluation alone.

Checking for the unusual chromosome feature is done through **amniocentesis**, a procedure that collects the developing fetus's cells for evaluation. But this test is not typically recommended, because not all affected individuals have this chromosome finding. In addition, the chromosome is not always evident in the cells from the amniotic fluid.

As of 2001 there was no accurate prenatal test to diagnose the syndrome during pregnancy.

After a baby is born with characteristics of Roberts SC phocomelia syndrome, a diagnosis can be made through a complete physical examination. In addition, analysis of the baby's chromosomes may also be useful. The chromosomes can be analyzed through a blood or tissue sample.

Treatment and management

At this time there is no treatment available for individuals with Roberts SC phocomelia syndrome. The shortness or absence of limbs makes it difficult for any type of limb-lengthening therapies to be useful in most instances.

Prognosis

The majority of severely affected individuals will die in the womb, or during or shortly after birth. Those who survive will have very obvious growth deficiency as well as mental retardation. Babies who are not as severely affected, with less dramatic limb shortening and no facial cleft, have a better overall prognosis.

Resources

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Katherine Susan Hunt, MS

Roberts syndrome *see* **Roberts SC phocomelia**

Robin sequence *see* **Pierre-Robin sequence**

Robinow dwarfism *see* **Robinow syndrome**

Robinow syndrome

Definition

Robinow syndrome encompasses two different hereditary disorders, both rare, with a similar pattern of physical abnormalities. Typical features of these conditions include mild to moderate short stature, distinctive facial features, skeletal abnormalities, and abnormal development of the genitalia.

Description

A family that included several individuals with a characteristic pattern of facial features, accompanied by short stature (dwarfism), skeletal abnormalities, and underdevelopment (hypoplasia) of the external genitalia (sex organs) was first described in 1969 by Dr. Meinhard Robinow. He named the condition "Fetal face syndrome," because the facial features are similar to those of a normal fetus. Only later was Dr. Robinow's name used to identify the syndrome. Other names for the condition include Robinow dwarfism, as well as "acral dysostosis with facial and genital abnormalities."

Skeletal abnormalities of varying types and severity occur in every case of Robinow syndrome. Most people with the condition have abnormal development of specific bones of the arms and legs resulting in some degree of short stature. Spinal abnormalities are also common. Most females are fertile, but only a few males with the condition have had children.

Genetic profile

Chromosomes are the microscopic structures inside cells that carry the genes. Each cell of the body contains 46 chromosomes in 23 pairs. The exceptions are sperm and eggs, which normally carry 23 chromosomes—one of each pair. The first 22 pairs of chromosomes in humans are known as the autosomes. An inherited condition is autosomal if the abnormal **gene** that causes it resides on one of the first 22 pairs of chromosomes.

Several years after Dr. Robinow's first report, it became clear that some families affected by Robinow syndrome have an autosomal dominant pattern of **inheritance**, while in other families the syndrome is inherited as an autosomal recessive trait. As of 2000, the reason for this genetic discrepancy was unknown.

Dominant inheritance means that an error in only one gene of a pair is enough to produce symptoms of the disorder. In other words, the abnormally functioning gene of the pair is dominant over the normal gene. A person who carries the gene for autosomal dominant Robinow syndrome has a 50% chance of passing it on to each of his or her offspring.

In autosomal recessive inheritance, a person must have errors in both copies of a gene pair in order to be affected. Someone who carries just one copy of the disease gene has another normally functioning gene of that pair to compensate for it. Therefore, a carrier of a single recessive gene typically shows no symptoms of the disorder. If two people who both carry the gene for recessive Robinow syndrome conceive a pregnancy, there is a 25% chance that they will each contribute the Robinow syndrome gene and have an affected child.

KEY TERMS

Acromelic—The anatomical term used to denote the end of a limb (arm or leg). In the context of Robinow syndrome, it refers to bones of the hands and feet.

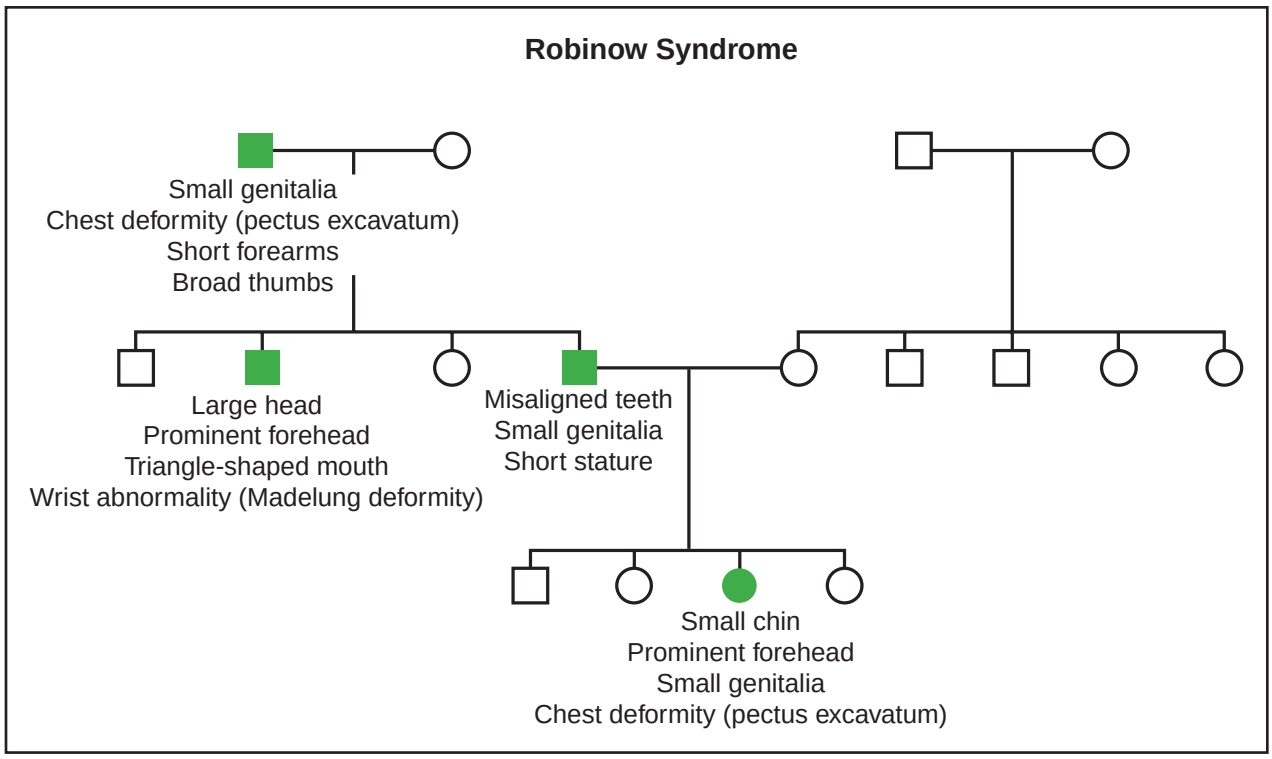
Brachymelia—A general medical term used to describe short limbs.

Hypertelorism—A wider-than-normal space between the eyes.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Mesomelic—The anatomical term used to describe the middle of a limb. The bones that constitute the middle of the arm are the radius and ulna, and mesomelic bones of the leg are the tibia and fibula.

Vertebra—One of the 23 bones which comprise the spine. *Vertebrae* is the plural form.



(Gale Group)

Mutations in the ROR2 gene are responsible for recessive Robinow syndrome. As of 2000, the exact function of the protein encoded by the ROR2 gene had not been determined, and the gene responsible for dominant Robinow syndrome had not been located.

Demographics

Both the dominant and recessive forms of Robinow syndrome are rare. Dominant Robinow syndrome does not appear to occur more frequently in any particular ethnic group. A significant proportion of recessive Robinow syndrome cases, however, have occurred in Czechoslovakia, Turkey, and the Middle East. In addition, some children with recessive Robinow syndrome have parents who are genetically related (consanguineous), such as first cousins. Parental consanguinity is sometimes seen in rare, autosomal recessive conditions, since people who are genetically related are more likely to carry the same recessive gene(s).

Signs and symptoms

The signs and symptoms of Robinow syndrome can be grouped into those that involve the face, those that affect the skeleton, and those affecting the genitalia. There is a good deal of overlap of symptoms between the dominant and recessive forms. In general, however, people with recessive Robinow syndrome tend to be more severely affected.

The facial features of Robinow syndrome include a flat nasal bridge, slightly upturned nose, triangular-shaped mouth, protruding forehead (frontal bossing), wide space between the eyes (hypertelorism), wide eye openings, low-set ears, long philtrum (groove from nose to upper lip), small lower jaw (micrognathia), excessive growth of the gums, and crowding of teeth.

People with Robinow syndrome have what is known as *acromesomelic brachymelia*. Acromesomelic refers to bones at the end (acro) and in the middle (meso) of the limbs. Brachymelia is the medical term for short limbs. Thus, short limbs in Robinow syndrome are due to shortened bones in the hands, feet, lower arms, and lower legs. Dominant Robinow syndrome is associated with normal height to borderline short stature, while recessive Robinow syndrome always results in short stature. Abnormalities of the spine often involve misshapen or fused vertebrae (so-called segmentation defects), as well as **scoliosis**. Vertebral abnormalities are more frequent and more pronounced in the recessive form of Robinow syndrome. Ribs may be fused together or abnormally shaped, and this may lead to pectus excavatum (sunken breastbone).

Males with Robinow syndrome typically have a hypoplastic penis, and may have undescended testicles

(cryptorchidism). Females can have a small clitoris and hypoplastic labia. A dysfunctional sex-steroid response-and-feedback mechanism may be partly to blame for some of the signs of Robinow syndrome, particularly the genital anomalies.

Physical anomalies found less frequently in Robinow syndrome include heart defects, kidney abnormalities, cleft lip/palate, and hearing loss. Most individuals with Robinow syndrome have normal intelligence, but a few have mild mental retardation.

Diagnosis

The diagnosis of Robinow syndrome is made by physical examination. Several other genetic syndromes have some of the same physical signs as Robinow syndrome, which can make arriving at the correct diagnosis more difficult. However, the pattern of skeletal abnormalities in Robinow syndrome has a distinct appearance when seen on x rays, which may help in confirming the diagnosis. Testing of the ROR2 gene is theoretically possible for recessive Robinow syndrome, but would only be offered on a research basis, if at all. As of 2000, there were no laboratory tests available to aid in the diagnosis of dominant Robinow syndrome.

Treatment and management

There is no cure for either type of Robinow syndrome. Future research may help to determine if some type of hormone therapy can be used to treat the short stature and/or hypoplastic genitalia. Otherwise, no specific protocol is recommended for managing children and adults with either form of the condition. An orthopedic surgeon might be needed to address any problems that arise related to skeletal abnormalities, especially in the spine. Special educational intervention would be indicated for anyone with learning disabilities or mental retardation.

People with pronounced physical signs of the condition (short stature and facial features) may have difficulties with their self-image. Males with a hypoplastic penis can present a special problem. In those cases, added psychological and social support is particularly important. **Genetic counseling** should be offered to individuals/families affected by Robinow syndrome to help them understand the condition, its inheritance, and any testing (including prenatal) that might be available.

Prognosis

Any one person with Robinow syndrome may have a good prognosis, depending on how well they cope with their particular symptoms. A child with recessive Robinow syndrome is more likely to have long-term difficulties than a child with the dominant form of the condition, but no blanket statements can be made. Overall, life span should not be significantly decreased in most cases of Robinow syndrome, since the majority of affected individuals do not have life-threatening complications.

Resources

BOOKS

Jones, Kenneth Lyons. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia: W.B. Saunders Company, 1997.

ORGANIZATIONS

Robinow Syndrome Foundation. PO Box 1072, Anoka, MN 55303. (612) 434-1152. <http://www.robinow.org>.

OTHER

"Robinow syndrome." National Library of Medicine (NLM). *MedlinePlus.* <http://medlineplus.nlm.nih.gov/mesh/jablonski/syndromes/syndrome_cgi?index=562.htm>.

Scott J. Polzin, MS

Robinow-Silverman-Smith syndrome *see* **Robinow syndrome**

Robinow-Sorauf syndrome *see* **Saethre-Chotzen syndrome**

Romano-Ward syndrome *see* **Long-QT syndrome**

Rothmund-Thomson syndrome

Definition

Rothmund-Thomson syndrome (RTS) is an extremely rare inherited disorder that appears in infancy and features skin degeneration (atrophic dermatosis), clouding of the lenses of the eyes (juvenile cataracts), skeletal abnormalities, short stature, and an increased risk of skin and bone cancers.

Description

Rothmund-Thomson syndrome is usually first apparent between three and six months of age. This disorder is characterized by early sun sensitivity and progressive degeneration or wasting (atrophy) of the skin as well as scarring and abnormal pigmentation of the skin. Other characteristic signs include sparse hair, clouding of

KEY TERMS

Alopecia—Loss of hair or baldness.

Atrophic dermatosis—Wasting away of the skin.

Depigmentation—Loss of pigment or skin color.

Dysplastic—The abnormal growth or development of a tissue or organ.

Edema—Extreme amount of watery fluid that causes swelling of the affected tissue.

Frontal bossing—A term used to describe a rounded forehead with a receded hairline.

Hyperpigmentation—An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

Hypogonadism—Small testes in men and scarse or irregular mentruation for females.

Keratosis—A raised thickening of the outer horny layer of the skin.

Microdontia—Small teeth.

Poikiloderma—A condition characterized by skin atrophy, widening of the small blood vessels (telangiectasia), and pigment changes giving a mottled appearance.

Prognathism—A protruding lower jaw.

Saddle nose—A sunken nasal bridge.

Telangiectasia—An abnormal widening of groups of small blood vessels in the skin.

the lenses of the eyes (juvenile cataracts), short stature, malformations of the face and head, teeth, nails, and bone, and other physical abnormalities. In rare cases, mental retardation may be present.

The syndrome was first described in 1868 by August von Rothmund, a German ophthalmologist, and in both 1923 and 1936 by Matthew S. Thomson, a British dermatologist. Both independently noted a familial disorder with cataracts, saddle nose, and skin degeneration. It is believed that Thomson's finding was the same disease that was seen long before by Rothmund. Other names for Rothmund-Thomson syndrome include poikiloderma congenita and poikiloderma atrophicans with cataract.

Genetic profile

Rothmund-Thomson is attributed to a mutation in a **gene** located on chromosome 8. Mutations in the gene RecQL4 (chromosomal locus 8q24), also called the Rothmund-Thomson gene, have been identified in four patients with Rothmund-Thomson syndrome.

Rothmund-Thomson syndrome is inherited as an autosomal recessive trait. This means that both parents have one copy of the Rothmund-Thomson gene but do not have the disease. Each of their children has a 25% chance of not having the gene, a 50% chance of having one Rothmund-Thomson gene (and, like the parents, being unaffected), and a 25% risk of having both Rothmund-Thomson genes and the disease.

Demographics

There is no specific population group that is at greater risk for this disorder, although it is more common in women (2:1). Evidence of Rothmund-Thomson syndrome has been found to occur in all races and many nationalities. The majority of affected people are from full-term pregnancies. As of the year 2001, a total of approximately 250 cases have been reported in English-speaking medical literature. The number of carriers for Rothmund-Thomson syndrome is unknown.

Signs and symptoms

The major characteristics of Rothmund-Thomson syndrome are skin abnormalities, short stature, juvenile cataracts, small hands, and delayed activities of the ovaries in females or testes in males. Symptoms vary from individual to individual.

Skin abnormalities usually appear in infancy, between three and six months of age. Skin changes begin as red inflamed patches, occasionally with blistering, on the cheeks along with swelling and then spread to other areas of the face, the arms and legs, and buttocks. Skin inflammation eventually subsides and a condition develops known as poikiloderma, characterized by abnormal widening (dilation) of groups of small blood vessels (telangiectasia), skin tissue degradation (atrophy), and patchy areas of abnormally decreased and/or unusually increased brown pigmentation (depigmentation and hyperpigmentation), giving the skin a mottled look. Skin that is exposed to the sun usually shows greater abnormalities. Sun sensitivity typically continues throughout the affected person's life. Those with extreme sun sensitivity can develop thickening of the skin (keratosis) of the face, hands, and feet, or cancerous skin changes later in life. Affected individuals are at increased risk of developing skin cancers (basal cell carcinoma and squamous cell carcinoma) and bone **cancer** (osteosarcoma).

There are many other physical abnormalities that affect people with Rothmund-Thomson syndrome. Juvenile cataracts, the clouding of the lenses of the eyes, develop in almost half of the people with RTS between the ages of four and seven. Severe growth delays result in short stature throughout life. Skeletal abnormalities such as unusually small hands and feet are common. Less typical are stubby fingers and toes, underdeveloped (hypoplastic) or absent thumbs, and/or underdeveloped (hypoplastic) or missing forearm bones (ulna and radii). Hypogonadism, the deficient activity of the ovaries in females or testes in males, causes irregular menstruation in females, and delayed sexual development and reduced fertility in both males and females. Facial skeletal abnormalities include a triangular-shaped face with a prominent forehead (frontal bossing), a sunken nasal bridge (saddle nose), and a protruding lower jaw (prognathism). Scalp hair is usually thin and fine, although alopecia (balding) occasionally occurs in early childhood. Often the eyebrows and eyelashes are sparse or absent. Dental abnormalities include excessive cavities, unusually small teeth (microdontia), or delayed or failure of teeth to erupt. Dysplastic, or abnormally developed nails are also seen in many people with Rothmund-Thomson syndrome.

Diagnosis

A diagnosis of Rothmund-Thomson syndrome is made based on clinical examination. There are no laboratory diagnostic tests. Mutations of the RecQL4 gene have been found in a few individuals with RTS. However, as of the year 2001, **genetic testing** is still on a research basis and is not available for diagnostic purposes.

There are no published diagnostic criteria. Diagnosis is usually based on the presence of the characteristic poikilodermatous rash in childhood, along with one or more of the following features: small stature, sparse or absent hair, cataracts, and cancer.

Treatment and management

Essential management of Rothmund-Thomson syndrome includes avoiding sun exposure and diligently using sunscreen that has both UVA and UVB protection.

An ophthalmologic evaluation for the detection and management of cataracts is recommended for affected people on an annual basis up to age 15. Surgical removal of significant cataracts may be necessary.

Because skin cancer is a risk, it is important to monitor the affected individual closely for lesions with unusual color or texture. They should also be watched carefully for any signs and symptoms of osteosarcoma, a cancerous bone tumor, including bone pain, swelling, or a growing lesion on the arms or legs.

Pulsed-dye laser therapy has been used to treat the widening of small blood vessels (telangiectases). Medications called retinoids can reduce the potential for skin cancer. Keratolytic drugs are used to cause thick skin to swell, soften, and then fall away.

Prognosis

Individuals with Rothmund-Thomson syndrome usually have a normal life span, although an increased risk for bone and skin cancer has been found. Most affected individuals will have normal intelligence, however learning disabilities and mental retardation have been reported in a small number of patients.

Resources

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Starr D. G., et al. "Non-Dermatological Complications and Genetic Aspects of the Rothmund-Thomson Syndrome." *Clinical Genetics* 27 (1985): 102–104.

ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

Plon, Sharon E., MD, PhD, and Lisa L. Wang, MD. (October 6, 1999). "Rothmund-Thomson syndrome." *GeneClinics.* University of Washington, Seattle. <http://www.geneclinics.org/profiles/rts>.

Nina B. Sherak, MS, CHES

RSH syndrome *see* **Smith-Lemli-Opitz syndrome**

RSH/SLO syndrome *see* **Smith-Lemli-Opitz syndrome**

Rubinstein syndrome *see* **Rubinstein-Taybi syndrome**

Rubinstein-Taybi syndrome

Definition

Rubinstein-Taybi syndrome is a rare genetic disorder involving mental retardation, short stature, broad thumbs and great toes, and characteristic facial features. First described in 1963 by the American physicians Dr. Jack Rubinstein and Dr. Hooshang Taybi, over 550 cases have since been reported.

KEY TERMS

Great toe—The first and largest toe on the foot.

Hallux—The great toe.

Recurrence risk—The possibility that the same event will occur again.

Respiratory—Having to do with breathing.

Description

The clinical picture of Rubinstein-Taybi syndrome (RSTS) is highly variable. The most prominent features include mental retardation, thumb and great toe abnormalities, and distinct facial characteristics.

Rubinstein-Taybi syndrome may also be referred to as broad-thumb-hallux syndrome or Rubinstein syndrome. The abbreviation for Rubinstein-Taybi syndrome is denoted "RSTS" or "RTS," although "RSTS" is preferred so as not to be confused with other syndromes such as **Rett syndrome** and Rothmund-Thompson syndrome.

Genetic profile

A change in a particular **gene**, known as the CREB binding protein (CBP) gene, causes RSTS. This gene is located on chromosome 16. Its position is denoted as 16p13.3 where p represents the short arm of the chromosome and 13.3 indicates the exact location on the arm.

CBP codes for a protein known as the human cyclic AMP regulated enhancer binding protein (CREBBP). CREBBP has many functions within a cell. Its general role is to regulate multiple pathways and the work of other genes. It is thought that this multifunctional aspect of CREBBP is what causes the diffuse abnormalities observed in RSTS.

RSTS is thought to be autosomal dominant. Only one copy of the CBP gene must be changed or mutated for a person to have RSTS. Most cases of RSTS are sporadic. That is, the majority of affected individuals do not have a parent with RSTS, rather RSTS arose due to a new mutation in the CBP gene. Sporadic mutations in genes occur by chance. They are rare and there is nothing a person can do during a pregnancy to cause or prevent them.

Demographics

The incidence of RSTS has been estimated at between one in 125,000 and one in 300,000 live births. Males and females are affected equally. Cases of RSTS have been observed throughout the world. Although RSTS is thought to be a rare disease, more cases are being diagnosed each year. In part, this is thought to be due to physicians' increasing awareness of the signs and symptoms involved in RSTS.

Signs and symptoms

RSTS is a genetic disorder involving primarily physical malformations and mental retardation.

Babies with RSTS may be born small compared to other newborns. They often have trouble feeding and may need to be assisted in this area. In conjunction with feeding problems, there may be respiratory (breathing) difficulties.

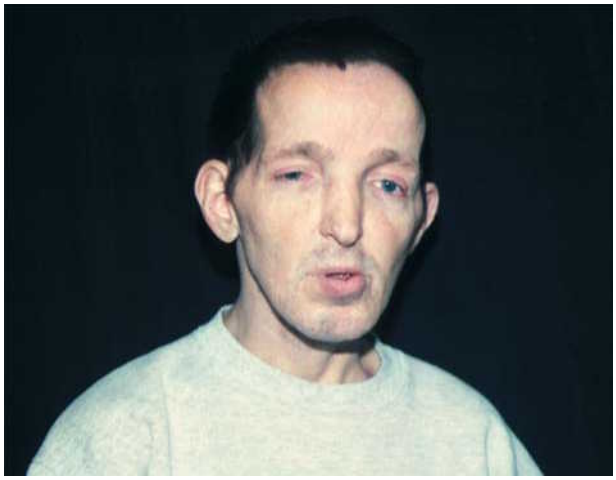
As the child matures, growth remains delayed, with short stature persistent throughout life. An average height of 60 in (153 cm) in males and 58 in (147 cm) in females and an average weight of 106 lb (48 kg) in males and 120 lb (55 kg) in females has been reported.

Developmental milestones are usually delayed. Although most children with RSTS learn to walk and talk, they tend to develop these skills much later than their peers. For example, the average age at which children with RSTS learn to walk is 30 months, compared to 12 months in unaffected children.

There are several unique physical characteristics associated with RSTS. Typical facial features include down-slanting eyes, beaked nose, and the fleshy septum of the nose extending beyond the nostrils. By two to three years of age, most affected children grow into what is considered the classic physical picture of RSTS. Because of their similar facial appearances, they may resemble other children with RSTS as much as or more than they resemble family members.

The most well known features of patients with RSTS are the broad thumbs and great toes (halluces). This finding may be observed at birth although some patients with RSTS have only broad thumbs, only broad toes, or neither.

Other findings that occur on a less frequent basis include malignant (cancerous) and benign (non-cancer-



Patients with Rubinstein-Taybi syndrome have very distinct facial characteristics such as down-slanting eyes, beaked nose, and the fleshy septum of the nose extending beyond the nostrils. *(Greenwood Genetic Center)*

ous) tumors, chronic ear infections, early onset of breast development in females, kidney abnormalities, high arched palate (roof of the mouth), malformed teeth (named talon cusps after their shape), heart defects, small head, and short upper lip with a pouting bottom lip.

Mental retardation of varying degrees is a constant in RSTS. Affected individuals may present mild to severe mental retardation. They have particular difficulty in expression through speech. Although affected individuals are usually able to understand what is spoken to them, they have a difficult time responding with spoken words. In general, it has been observed that many patients with RSTS do not progress beyond a first-grade level.

It has been noted that affected individuals tend to have happy, outgoing, and energetic personalities. They have been described as people who "know no strangers." People with RSTS tend to smile often, although, due to their physical differences, this smile is sometimes described as a grimace.

Not every person with RSTS will have all of the aforementioned medical, physical, and social characteristics. Although people with RSTS have much in common, it is important to remember that each person is unique with his or her own qualities and challenges.

Diagnosis

Diagnosis is usually based on clinical findings. Laboratory techniques for definitive diagnosis by DNA analysis are available, but at this time are only able to identify approximately 25% of affected individuals. This is due to the considerable number of different changes within the same gene that all may lead to RSTS.

Prenatal diagnosis is available for RSTS; however, again, only approximately 25% of cases are picked up by current available techniques. Because the physical features associated with RSTS are difficult to distinguish prenatally, and the available DNA test does not identify most cases, the vast majority of individuals with RSTS are diagnosed after birth.

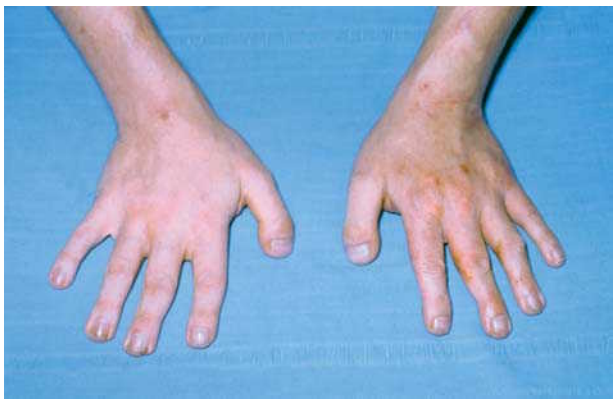
The age at which a person is diagnosed varies from patient to patient due to the range in severity of clinical findings. Those with a more mild presentation tend to be diagnosed later in life. Diagnosis may be more difficult in non-Caucasian persons due to the great majority of research and published data having been done on Caucasian patients.

Studies have been conducted in an effort to better identify individuals with RSTS. In 2000, the outcome of a study aimed at improving laboratory techniques for RSTS diagnosis was published. The data suggested that it soon may be possible to identify more affected individuals by DNA analysis both prenatally (before birth) and postnatally (after birth).

Misdiagnosis is sometimes made between RSTS and **Saethre-Chotzen syndrome** because of their similar clinical findings.

A correct diagnosis is important when providing a family with **genetic counseling**. A family with a child with RSTS can have many questions. Genetic counseling may be helpful in providing the family with some answers, including information about the risk of having another child with RSTS.

In general, a recurrence risk of 0.1% is given to couples that have had one child with RSTS. For individuals



Broad thumbs is the most well known feature of RSTS. *(Greenwood Genetic Center)*

with RSTS there is 50% chance of passing the condition on in each pregnancy.

Treatment and management

Treatment and management is aimed at encouraging and supporting cognitive development and alleviating medical symptoms. There is no cure for Rubinstein-Taybi syndrome.

Medical problems, such as ear and respiratory infections, are treated as they occur. Chronic ear infections may lead to hearing loss and it is therefore important to have this infection treated as quickly as possible.

Early intervention and occupational and physical therapy are encouraged along with behavioral management. It has been shown that children with mental retardation and developmental delay, due to any cause, benefit from these therapies. In particular, for children with RSTS, speech therapy and alternate forms of communication, such as sign language, have been found to be helpful. Alternative avenues of communication may help children with RSTS express their thoughts and feelings and reduce the frustration they may feel at not being understood verbally.

Prognosis

Prognosis is variable due to the wide range of presentations among affected individuals. Mental retardation and developmental delay may range from mild to severe, with a reported average IQ of 51 (the general population average IQ is 100). Medical problems also vary in number and severity.

Most individuals with RSTS will have a normal life span. As adults, affected individuals may live in group homes or supervised apartments. Many work in sheltered workshops or in supervised employment situations.

Individuals with RSTS are capable of having children of their own. In a study of 502 individuals with RSTS, two had reproduced. In total they had three children, one affected with RSTS and two unaffected. It has also been the case that a very mildly affected woman was not diagnosed with RSTS until her child was born with the same disorder.

Resources

PERIODICALS

Baxter, Garry, and John Beer. "Rubinstein-Taybi Syndrome." *Psychological Reports* 70, no. 2 (April 1992): 451–56.

ORGANIZATIONS

Rubinstein-Taybi Parent Support Group. c/o Lorrie Baxter, PO Box 146, Smith Center, KS 66967. (888) 447-2989. lbaxter@ruraltelnet. <http://www.specialfriends.org>.

WEBSITES

Online Rubinstein-Taybi Pamphlet. <http://www.rubinstein-taybi.org/html/pamplet.html>.
Rubinstein-Taybi Website. <http://www.rubinstein-taybi.org>.
The Arc—A National Organization on Mental Retardation. <http://www.thearc.org>.

Java O. Solis, MS

Russell-Silver syndrome

Definition

Russell-Silver syndrome (RSS) is one of the recognized forms of intrauterine growth retardation (IUGR) diseases. It was first independently described by H. K. Silver in 1953 and by A. Russell in 1954.

Description

Russell-Silver syndrome is one of more than 300 recognized forms of **genetic disorders** that lead to short stature. It is characterized by:

- the presence of a triangular shaped face
- an incurving fifth finger (clinodactyly)
- low birth weight and length (intrauterine growth retardation, or IUGR)
- a poor appetite in the first few years of life

This disorder is alternately known as Russell syndrome, Silver syndrome, or Silver-Russell syndrome. Some clinicians use the term Russell syndrome to indicate this disorder when the size of the sides of the body and the limbs are equal, and the term Silver syndrome to indicate this disorder when the size of the sides of the body or the length of the limbs is different (body asymmetry).

Genetic profile

The exact genetic cause, or causes, of RSS have not been fully identified in early 2001. It is currently believed that almost all cases of RSS are the result of mutations on a **gene**, or possibly more than one gene, on chromosome 7.

Demographics

RSS occurs in approximately one in every 200,000 live births. Almost all cases of RSS are sporadic, that is, they appear for the first time in individuals with no fam-

ily history of RSS. However, case studies indicating all three modes of inheritance—autosomal recessive, autosomal dominant, and X-linked—have been reported.

RSS does not appear to affect any particular race or ethnic group in a greater frequency than others. It is also observed equally in males and females.

Signs and symptoms

There are six characteristics that define Russell-Silver syndrome: a triangular shaped face; down turned corners of the mouth; inwardly curved little fingers (clinodactyly); a combination of low birth weight (intrauterine growth retardation) and short birth length after a full term gestation; a long, narrow head (scaphocephaly); and a poor appetite that causes slow growth after birth. These characteristics are commonly observed in people affected with RSS.

Several other characteristics are found in most, but not all, RSS affected individuals. These include:

- low blood sugar (hypoglycemia) in infancy and early childhood
- unequal body and limb size from one side of the body to the other (body asymmetry)
- late closure of the soft spot in the front of the skull
- a broad forehead
- a small chin and jaw
- crowding of the teeth or abnormally small teeth caused by a smaller than normal jaw
- an abnormally thin upper lip
- low-set, small, and prominent ears
- fusion or webbing of the toes (syndactyly)
- poor muscle tone (hypotonia)
- a condition in which the bones are not as mature as the bones of a typical person of the same age (delayed bone age)
- developmental delays

In males affected with RSS, undescended testicles and a misplacement of the urethral opening (hypospadias) on the bottom of the penis rather than on the tip of the glans is often seen.

People affected with RSS may show other symptoms on a less uniform basis. These include:

- water on the brain
- a bluish coloration of the whites of the eyes
- a highly-arched palate
- an absence of certain teeth
- frequent ear infections caused by fluid in the ear, which can lead to temporary hearing loss
- migraine headaches
- a curvature of the spine (**scoliosis**) or other problems with the spine, often caused by body asymmetry
- abnormalities of the kidneys
- an abnormally early onset of puberty (precocious puberty)
- irregularly colored spots on the skin (café-au-lait spots)

KEY TERMS

Body asymmetry—Abnormal development of the body in which the trunk and/or the limbs are not of equal size from one side of the body to the other.

Clinodactyly—An abnormal inward curving of the fingers or toes.

Delayed bone age—An abnormal condition in which the apparent age of the bones, as seen in x rays, is less than the chronological age of the patient.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Intrauterine growth retardation—A form of growth retardation occuring in the womb that is not caused by premature birth or a shortened gestation time. Individuals affected with this condition are of lower than normal birth weight and lower than normal length after a complete gestation period.

Precocious puberty—An abnormal condition in which a person undergoes puberty at a very young age. This condition causes the growth spurt associated with puberty to occur before the systems of the body are ready, which causes these individuals to not attain normal adult heights.

Russell syndrome—An alternative term for Russell-Silver syndrome. Many doctors use this term to mean a Russell-Silver syndrome affected individual who does not have body asymmetry.

Scaphocephaly—An abnormally long and narrow skull.

Silver syndrome—An alternative term for Russell-Silver syndrome. Many doctors use this term to mean an individual with Russell-Silver syndrome who also has body asymmetry.

- high energy levels
- attention deficit disorder (ADD)
- fainting spells

Diagnosis

Diagnosis of RSS is generally accomplished by performing a genetic test on cells grown from a skin sample. This test must be performed prior to the fifth year of life and it is not always accurate.

A diagnosis of RSS is supported by examination of the affected individual's growth curve and daily food intakes. In a child affected with RSS, these will fall well short of the mean for children of the same age.

Body measurements for asymmetry and x rays to determine the bone age versus the actual age of the patient are also useful. Additionally, a blood test indicating hypoglycemia may indicate RSS. When RSS is suspected in males, an examination of the genitals may reveal undescended testicles or a misplacement of the urethral opening.

Treatment and management

Treatment of RSS varies on a case-by-case basis depending on the symptoms of the affected individual.

Dietary changes to increase food intake are required by all people with RSS. Many patients with RSS also require a diet high in sugars to treat hypoglycemia. When the necessary food intake can not be accomplished by dietary changes, it may be necessary to treat patients with the antihistamine periactin, which also serves as an appetite stimulant. Some patients may also benefit from a feeding pump or gastrostomy. Gastrostomy is a surgical procedure in which a permanent opening is made directly in the stomach for the introduction of food.

In cases of severe growth retardation, certain people will require the administration of an artificial form of growth hormone (recombinant growth hormone) to stimulate growth, increase the rate of growth, and to increase their final adult height.

Ear tubes may be required to improve fluid drainage from the ears of some patients affected with RSS.

In cases of body asymmetry, limb lengthening surgeries may be recommended. Alternatively, shoe lifts may be all that is necessary for the attainment of a normal gait.

Depending on the severity of physical, emotional, and psychological symptoms, some affected individuals may benefit from physical and/or occupational therapy. If ADD or other developmental problems exist, individuals with RSS may require educational assistance, such as remedial reading. In cases where the jaw is extremely small, talking may be difficult. These patients may require speech therapy.

Precocious puberty is the entrance of a child into puberty prior to the age of eight or nine. This early onset of puberty is generally accompanied by a growth spurt prior to puberty. While entering puberty before one is emotionally ready is certainly a serious problem, it is the growth spurt prior to puberty that is of major medical significance and concern.

If this growth spurt occurs prior to puberty, it is generally not as robust as if it had occurred during puberty, which causes the individual undergoing this growth spurt to grow less than a person who undergoes this process during puberty. The result is that a person who undergoes precocious puberty will generally end up much shorter in adulthood than his or her peers.

There are three hormonal therapies available in the United States to treat precocious puberty. Histrelin (trade name: Supprelin) is administered by daily injection. Leuprolide acetate (trade name: Lupron) is available as a depot formulation every four weeks. A depot formulation places medication in a tiny pump that is attached to the patient's body and releases the medication over time. Nafarelin acetate (trade name: Synarel) is administered as a nasal spray three times daily. Because of the age of people being treated, Lupron is most often the medication of choice because it is only administered once a month.

Some doctors have noticed that persons affected with RSS may have a slightly elevated chance of developing Wilm's tumor, the most common form of kidney **cancer**. Most cases of this type of cancer occur before the age of eight, and this condition is extremely rare in adults. It is important that children with RSS be screened with ultrasound every three months until the age of eight to make sure they have not developed Wilm's tumor. Wilm's tumor is quite treatable via surgery, chemotherapy, and/or radiation.

Prognosis

With proper medical treatment to address their individual symptoms, people affected with RSS do not, in general, have a reduced quality of life relative to the remainder of the population. As these people age, the symptoms of RSS tend to become less noticeable: the triangular shape of the face tends to lessen, muscle tone and coordination improve, appetite improves, speech improves, and learning occurs. An affected adult is generally not less happy and/or healthy than any other person.

Resources

ORGANIZATIONS

MAGIC Foundation for Children's Growth. 1327 N. Harlem Ave., Oak Park, IL 60302. (708) 383-0808 or (800) 362-4423. Fax: (708) 383-0899. mary@magicfoundation.org. <http://www.magicfoundation.org/ghd.html>.

Yahoo Groups: Russell-Silver syndrome Support Group. <http://groups.yahoo.com/group/RSS-Support>.

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Paul A. Johnson

S

Saethre-Chotzen syndrome

Definition

Saethre-Chotzen syndrome is an inherited disorder that affects one in every 50,000 individuals. The syndrome is characterized by early and uneven fusion of the bones that make the skull (cranium). This affects the shape of the head and face, which may cause the two sides to appear unequal. The eyelids are droopy; the eyes widely spaced. The disorder is also associated with minor birth defects of the hands and feet. In addition, some individuals have mild mental retardation. Some individuals with Saethre-Chotzen syndrome may require some medical or surgical intervention.

Description

Saethre-Chotzen (say-thre chote-zen) syndrome belongs to a group of rare **genetic disorders** with **craniosynostosis**. Craniosynostosis means there is premature closure of the sutures (seams) between certain bones of the cranium. This causes the shape of the head to be tall, asymmetric, or otherwise altered in shape (acrocephaly). There is also webbing (syndactyly) of certain fingers and toes. Another name for Saethre-Chotzen syndrome is acrocephalosyndactyly type III. It is one of the more mild craniosynostosis syndromes.

The story of Saethre-Chotzen syndrome goes back to the early 1930s. It was then that a Norwegian psychiatrist, Haakon Saethre wrote about a mother and two daughters in the medical literature. Each had a low frontal hairline; long and uneven facial features; short fingers; and webbing of the second and third fingers, and second, third, and fourth toes. A year later in 1931, F. Chotzen, a German psychiatrist, reported a family with similar features. However, these individuals were also quite short and had additional features of mild mental retardation and hearing loss.

Genetic profile

Saethre-Chotzen is usually found in several generations of a family. It is an autosomal dominant disorder and can be inherited, and passed on, by men as well as women. Almost all genes come in pairs. One copy of each pair of genes is inherited from the father and the other copy of each pair of genes is inherited from the mother. Therefore, if a parent carries a **gene mutation** for Saethre-Chotzen, each of his or her children has a 50% chance of inheriting the gene mutation. Each child also has a 50% chance of inheriting the working copy of the gene, in which case they would not have Saethre-Chotzen syndrome.

The search for the gene for Saethre-Chotzen syndrome is an interesting story. The first clue as to the cause of the disorder came in 1986, with the identification of patients who had a chromosome deletion of the short arm of chromosome 7. Linkage studies in the early 1990s narrowed the region for this gene to a specific site, at 7p21. Then, in 1996, scientists at Johns Hopkins Children's Center began to study a gene called TWIST as the candidate gene for Saethre-Chotzen syndrome. The TWIST gene was suspected because of earlier studies that showed how this gene works in the mouse.

The mouse TWIST gene normally works in forming the skeleton and muscle of the head, face, hands, and feet. Mice lacking both copies of the gene die before birth. Many have severe birth defects, including failure of the neural tube to close. They have an abnormal head and limb defects. However, mice with just one non-working copy of the TWIST gene did not die. Closer examination of these mice showed that they had only minor hand, foot and skull defects. The features were similar to those seen in Saethre-Chotzen syndrome.

It was also known that the mouse TWIST gene was located on chromosome 12 in mice, a location that corresponds to the short arm of chromosome 7 in humans. With this evidence, the researchers went on to map and isolate the human TWIST gene on human chromosome 7. They showed that this gene was in the same location

KEY TERMS

Acrocephaly—An abnormal cone shape of the head.

Chromosome deletion—A missing sequence of DNA or part of a chromosome.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Cranium—The skeleton of the head, which include all of the bones of the head except the mandible.

Exon—The expressed portion of a gene. The exons of genes are those portions that actually chemically code for the protein or polypeptide that the gene is responsible for producing.

Linkage—The association between separate DNA sequences (genes) located on the same chromosome.

Syndactyly—Webbing or fusion between the fingers or toes.

Transcription—The process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

Transcription factor—A protein that works to activate the transcription of other genes.

that was missing in some individuals with Saethre-Chotzen. The TWIST gene is a small gene, containing only two exons (coding regions). Upon searching for alterations (mutations) in the TWIST gene, they found five different types of mutations in affected individuals. Since none of these mutations were found in unaffected individuals, this was proof positive that the TWIST gene was the cause of Saethre-Chotzen syndrome.

Scientists have also used animal models and the fruit fly Drosophila, to study the function of the TWIST gene. They have found that it takes two TWIST protein molecules to combine together, in order to function as a transcription factor for **DNA**. The normal function of the TWIST protein is to bind to the DNA helix at specific places. By doing so, it works to regulate which genes are activated or "turned on". Most of the mutations identified in the TWIST gene so far seem to interfere with how the protein product binds to DNA. In effect, other genes that would normally be activated during development of the embryo may in fact not be turned on.

More recent studies suggest that the TWIST protein may induce the activation of genes in the fibroblast growth factor receptor (FGFR) pathway. Mutations in the FGFR family of genes cause other conditions with craniosynostosis such as **Crouzon syndrome**. Crouzon syndrome, like Saethre-Chotzen syndrome, is a mild craniosynostosis disorder. There is much overlap in the features of the face and hands in each condition. In fact, some patients initially thought to have Saethre-Chotzen were given a new diagnosis of Crouzon syndrome after studying both the TWIST and the FGFR genes for mutations.

In all, it is thought that the TWIST protein most likely acts to turn on the FGFR genes. These genes, in turn, instruct various cells of the head, face, and limb structures to grow and differentiate. If the TWIST gene or other genes of the FGFR pathway are altered, an individual will have one of the craniosynostosis syndromes.

Demographics

Saetre-Chotzen syndrome affects both males and females equally. It most likely occurs in every racial and ethnic group. Approximately one or two in every 50,000 individuals has Saetre-Chotzen syndrome, making it the most common of the craniosynostosis syndromes.

Signs and symptoms

The cranium is made up of three main sections. The three sections are the face, the base of the cranium, and the top and sides of the head. Most of the cranium assumes its permanent shape before birth. However, the bones that make up the top and side of the head are not fixed in place, and the seams between the bones (cranial sutures) remain open. This allows the top of the head to adjust in shape, as the unborn baby passes through the narrow birth canal during labor. After birth, the cranial sutures will close, most often within the first few years of life. The shape of the cranium is then complete.

In Saethre-Chotzen, the shape of the cranium is abnormally formed. The reason is that the coronal suture closes too early, sometimes even before birth. The coronal suture separates the two frontal bones (forehead) from the parietal bones (top of the head). If the early closure is unilateral or asymmetric, then the forehead and face will form unevenly, from one side to the other. This also forces the top of the head to become more pointed, almost tower-like. The forehead looks high and wide. The face will appear uneven on each side, especially in the area of the eyes and cheeks.

There is also less space for the normal features of the face to develop. For instance, the eye sockets are more

shallow and the cheekbones are flat. This makes the eyes more prominent, and spaced further apart than normal. Adding to the unevenness of the face is drooping of the upper eyelids, and a slight down slant to the eyes. The nose may look beaked or bent slightly downward at the tip. In some individuals, the ears look small and low-set on the face.

The other main feature of the syndrome is minor abnormalities of the hands and feet. Webbing (syndactyly) commonly occurs between the second and third fingers and toes. The thumbs are short and flat. The fifth finger may be permanently curved or bent at the tip.

Each individual with Saetre-Chotzen is affected somewhat differently. The features are usually quite variable even within the same family. Most individuals are mildly affected. Their facial features may be somewhat flat and uneven, but not strikingly so. However, if more than one cranial suture closes too early (and this can happen in some individuals), there is more severe disfigurement to their face.

In addition to the physical characteristics, individuals with Saetre-Chotzen may have growth delays, leading to less than average adult height. Most individuals are of normal intelligence, although some may have mild to moderate mental retardation (IQ from 50-70). For the growth and mental delays, it becomes necessary to provide special assistance and anticipatory guidance.

Diagnosis

For many years, there was widespread discussion among physicians (geneticists) over whether a given patient would have either Saethre-Chotzen or Crouzon syndrome. There may even be confusion with other craniosynostosis syndromes or with isolated craniosynostosis. However, the availability of direct gene testing now allows for a more definitive diagnosis for these patients. Simply using a blood sample, a direct gene test for mutations in the TWIST gene can be done. If an individual also has mental retardation or other significant birth defects, it is suggested that they be screened more fully for deletions of the TWIST gene.

Treatment and management

Very often, the physical characteristics of Saethre-Chotzen are so mild that no surgical treatment is necessary. The facial appearance tends to improve as the child grows. However, sometimes surgery is needed to correct the early fusion of the cranial bones. A specialized craniofacial medical team, experienced with these types of patients, should do this surgery. Surgery may also be done to release the webbing of the fingers and toes.

Some of the more severely affected individuals with Saethre-Chotzen may experience problems with their vision. There may be less space in the eye socket due to the bone abnormalities of the face. This can lead to damage of the nerves of the eye and may require corrective surgery. The tear ducts of the eye can also be missing or abnormal. Re-constructive surgery is sometimes performed to correct the drooping of the eyelids or narrowing of the nasal passage.

Prognosis

Most individuals with Saethre-Chotzen syndrome appear to have a normal life span.

Resources

ORGANIZATIONS

Children's Craniofacial Association. PO Box 280297, Dallas, TX 75243-4522. (972) 994-9902 or (800) 535-3643. contactcca@ccakids.com. <http://www.ccakids.com>.

FACES: The National Craniofacial Association. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org>.

Forward Face, Inc. 317 East 34th Street, Room 901, New York, NY 10016. (212) 684-5860, (800) 393-3223.

MUMS. National Parent to Parent Organization. 150 Custer Court, Green Bay, WI 54301-1243. (920)336-5333. <http://www.netnet.net/mums>.

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Kevin M. Sweet, MS, CGC

Sanfilippo syndrome (MPS III) *see* **Mucopolysaccharidosis (MPS)**

Sarcoma-breast-leukemia-adrenal gland (SBLA) syndrome *see* **Li-Fraumeni syndrome**

SC syndrome *see* **Roberts SC phocomelia**

Scheie syndrome (MPS I) *see* **Mucopolysaccharidosis (MPS)**

Schilder disease *see* **Adrenoleukodystrophy (ALD)**

Schinzel acrocallosal syndrome *see* **Acrocallosal syndrome**

Schinzel-Giedion syndrome

Definition

Schinzel-Giedion syndrome, or Schinzel-Giedion Midface-Retraction syndrome is a rare malformation syndrome characterized by skeletal anomalies, a coarse face, urogenital defects, and severe mental retardation.

Description

In affected individuals, the ureter, or tube that carries urine from the kidney into the bladder, is obstructed causing the pelvis and kidney duct to become swollen with excess urine. This is called hydronephrosis. Other features of the syndrome include hypertrichosis or the excessive growth of hair, a flat midface, abnormal brain activity, skeletal abnormalities, and severe mental retardation.

Patients show abnormal bone maturation including broad and dense ribs and short arms and legs. Severely delayed mental and motor development is accompanied by seizures and spasticity.

Genetic profile

Some scientists have suggested that the syndrome is inherited as an autosomal recessive trait because they observed that the syndrome appeared in two sibs of different sex, which suggested autosomal-recessive **inheritance**. However, other researchers have hypothesized that Schinzel-Giedion syndrome may be a dominant disorder with gonadal mosaicism in one parent. Gonadal mosaicism can occur when either the testes or ovaries contain some cells with an extra chromosome. Scientists have also postulated that the syndrome may be caused by an unbalanced structural chromosome abnormality.

Demographics

Schinzel-Giedion syndrome is extremely rare and remains incompletely defined. About 25 to 30 well-documented cases have been reported beginning in 1978. The syndrome was originally observed in a brother, who lived less than 24 hours and a sister who survived for 16 months. Both displayed multiple skull abnormalities and profound midface retraction. They each had **congenital heart defects**, hydronephrosis, **clubfoot**, and hypertrichosis. Eight other cases, all sporadic, including two offspring of consanguineous parents were subsequently identified that year. Less than 30 cases are described in the medical literature detailing major and minor features of the syndrome. Only one case has been described in Japan. The other described cases have occurred in Western countries.

KEY TERMS

Hydronephrosis—Obstruction of the tube that carries urine from the kidney into the bladder causing the pelvis and kidney duct to become swollen with excess urine.

Signs and symptoms

Clinical signs include a flat midface, low set ears, a prominent forehead, skull abnormalities including large fontanels or openings, a short broad neck, genital malformations, congenital heart defects including atrial septal defect, clubfoot, and growth retardation.

Diagnosis

The detection of renal defects using prenatal ultrasound is one of the primary means of diagnosis. Clinical observation of coarse facial features, skeletal anomalies, and MRI studies aid diagnosis after birth. Serial cranial MRI studies that show a progressive neurodegenerative process affecting both gray and white matter typify Schinzel-Giedion syndrome. Clinical signs of abnormal cortical gray matter include seizures, **dementia**, and blindness in some cases. Abnormalities in the white matter can produce spasticity and hypereflexia.

Treatment and management

MRI studies indicate the syndrome is a progressive neurodegenerative process and patients have a limited life span. Nursing care and supportive measures are required to keep the patient comfortable.

Prognosis

Death prior to the second year of life represents the most common outcome.

Resources

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Shah, A.M., et al. "Schinzel-Giedion Syndrome: Evidence for a Neurodegenerative Process." *American Journal of Medical Genetics* 82 (1999): 344-347.

ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Julianne Remington

Schizophrenia

Definition

Schizophrenia is a psychotic disorder (or a group of disorders) marked by severely impaired thinking, emotions, and behaviors. Schizophrenic patients are typically unable to filter sensory stimuli and may have enhanced perceptions of sounds, colors, and other features of their environment. Most schizophrenics, if untreated, gradually withdraw from interactions with other people and lose their ability to take care of personal needs and grooming.

Description

The course of schizophrenia in adults can be divided into three phases or stages. In the acute phase, the patient has an overt loss of contact with reality (psychotic episode) that requires intervention and treatment. In the second or stabilization phase, the initial psychotic symptoms have been brought under control but the patient is at risk for relapse if treatment is interrupted. In the third or maintenance phase, the patient is relatively stable and can be kept indefinitely on antipsychotic medications. Even in the maintenance phase, however, relapses are not unusual and patients do not always return to full functioning.

The term schizophrenia comes from two Greek words that mean "split mind." It was observed around 1908, by a Swiss doctor named Eugen Bleuler, to describe the splitting apart of mental functions that he regarded as the central characteristic of schizophrenia.

Recently, some psychotherapists have begun to use a classification of schizophrenia based on two main types. People with Type I, or positive schizophrenia, have a rapid (acute) onset of symptoms and tend to respond well to drugs. They also tend to suffer more from the "positive" symptoms, such as delusions and hallucinations. People with Type II, or negative schizophrenia, are usually described as poorly adjusted before their schizophrenia slowly overtakes them. They have predominantly "negative" symptoms, such as withdrawal from others and a slowing of mental and physical reactions (psychomotor retardation).

The fourth (1994) edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) specifies five subtypes of schizophrenia.

Paranoid

The key feature of this subtype of schizophrenia is the combination of false beliefs (delusions) and hearing voices (auditory hallucinations), with more nearly normal emotions and cognitive functioning (cognitive functions include reasoning, judgment, and memory). The delusions of paranoid schizophrenics usually involve thoughts of being persecuted or harmed by others or exaggerated opinions of their own importance, but may also reflect feelings of jealousy or excessive religiosity. The delusions are typically organized into a coherent framework. Paranoid schizophrenics function at a higher level than other subtypes, but are at risk for suicidal or violent behavior under the influence of their delusions.

Disorganized

Disorganized schizophrenia (formerly called hebephrenic schizophrenia) is marked by disorganized speech, thinking, and behavior on the patient's part, coupled with flat or inappropriate emotional responses to a situation (affect). The patient may act silly or withdraw socially to an extreme extent. Most patients in this category have weak personality structures prior to their initial acute psychotic episode.

Catatonic

Catatonic schizophrenia is characterized by disturbances of movement that may include rigidity, stupor, agitation, bizarre posturing, and repetitive imitations of the movements or speech of other people. These patients are at risk for malnutrition, exhaustion, or self-injury. This subtype is presently uncommon in Europe and the United States. Catatonia as a symptom is most commonly associated with mood disorders.

Undifferentiated

Patients in this category have the characteristic positive and negative symptoms of schizophrenia but do not

meet the specific criteria for the paranoid, disorganized, or catatonic subtypes.

Residual

This category is used for patients who have had at least one acute schizophrenic episode but do not presently have strong positive psychotic symptoms, such as delusions and hallucinations. They may have negative symptoms, such as withdrawal from others, or mild forms of positive symptoms, which indicate that the disorder has not completely resolved.

Genetic profile

The risk of schizophrenia among first-degree biological relatives is ten times greater than that observed in the general population. Furthermore, the presence of the same disorder is higher in monozygotic twins (identical twins) than in dizygotic twins (nonidentical twins). The research concerning adoption studies and identical twins also supports the notion that environmental factors are important, because not all relatives who have the disorder express it. There are several **chromosomes** and loci (specific areas on chromosomes which contain mutated genes) that have been identified. Research is actively ongoing to elucidate the causes, types, and variations of these mutations.

Demographics

A number of studies indicate that about one percent of the world's population is affected by schizophrenia, without regard to race, social class, level of education, or cultural influences (outcome may vary from culture to culture, depending on the familial support of the patient). Most patients are diagnosed in their late teens or early twenties, but the symptoms of schizophrenia can emerge at any age in the life cycle. The male/female ratio in adults is about 1.2:1. Male patients typically have their first acute episode in their early twenties, while female patients are usually closer to age 30 when they are recognized with active symptoms.

Schizophrenia is rarely diagnosed in preadolescent children, although patients as young as five or six have been reported. Childhood schizophrenia is at the upper end of the spectrum of severity and shows a greater gender disparity. It affects one or two children in every 10,000; the male/female ratio is 2:1.

Signs and symptoms

Theories of causality

One of the reasons for the ongoing difficulty in classifying schizophrenic disorders is incomplete understanding of their causes. As of 1998, it is thought that these disorders are the end result of a combination of genetic, neurobiological, and environmental causes. A leading neurobiological hypothesis looks at the connection between the disease and excessive levels of dopamine, a chemical that transmits signals in the brain (neurotransmitter). The genetic factor in schizophrenia has been underscored by recent findings that first-degree biological relatives of schizophrenics are ten times as likely to develop the disorder as are members of the general population.

Prior to recent findings of abnormalities in the brain structure of schizophrenic patients, several generations of psychotherapists advanced a number of psychoanalytic and sociological theories about the origins of schizophrenia. These theories ranged from hypotheses about the patient's problems with anxiety or aggression to theories about stress reactions or interactions with disturbed parents. Psychosocial factors are now thought to influence the expression or severity of schizophrenia, rather than cause it directly.

Another hypothesis suggests that schizophrenia may be caused by a virus that attacks the hippocampus, a part of the brain that processes sense perceptions. Damage to the hippocampus would account for schizophrenic patients' vulnerability to sensory overload. As of mid-1998, researchers were preparing to test antiviral medications on schizophrenics.

Symptoms of schizophrenia

Patients with a possible diagnosis of schizophrenia are evaluated on the basis of a set or constellation of symptoms; there is no single symptom that is unique to schizophrenia. In 1959, the German psychiatrist Kurt Schneider proposed a list of so-called first-rank symptoms, which he regarded as diagnostic of the disorder.

These symptoms include:

- delusions
- somatic hallucinations
- hearing voices commenting on the patient's behavior
- thought insertion or thought withdrawal.

Somatic hallucinations refer to sensations or perceptions concerning body organs that have no known medical cause or reason, such as the notion that one's brain is radioactive. Thought insertion and/or withdrawal refers to delusions that an outside force (for example, the FBI, the CIA, Martians, etc.) has the power to put thoughts into one's mind or remove them.

Positive symptoms

The positive symptoms of schizophrenia are those that represent an excessive or distorted version of normal

KEY TERMS

Affective flattening—A loss or lack of emotional expressiveness. It is sometimes called blunted or restricted affect.

Akathisia—Agitated or restless movement, usually affecting the legs and accompanied by a sense of discomfort. It is a common side effect of neuroleptic medications.

Catatonic behavior—Behavior characterized by muscular tightness or rigidity and lack of response to the environment. In some patients, rigidity alternates with excited or hyperactive behavior.

Delusion—A fixed, false belief that is resistant to reason or factual disproof.

Depot dosage—A form of medication that can be stored in the patient's body tissues for several days or weeks, thus minimizing the risk of the patient forgetting daily doses. Haloperidol and fluphenazine can be given in depot form.

Dopamine receptor antagonists (DAs)—The older class of antipsychotic medications, also called neuroleptics. These primarily block the site on nerve cells that normally receive the brain chemical dopamine.

Dystonia—Painful involuntary muscle cramps or spasms.

Extrapyramidal symptoms (EPS)—A group of side effects associated with antipsychotic medications. EPS include parkinsonism, akathisia, dystonia, and tardive dyskinesia.

First-rank symptoms—A set of symptoms designated by Kurt Schneider in 1959 as the most important diagnostic indicators of schizophrenia. These symptoms include delusions, hallucinations, thought insertion or removal, and thought broadcasting. First-rank symptoms are sometimes referred to as Schneiderian symptoms.

Hallucination—A sensory experience of something that does not exist outside the mind. A person can experience a hallucination in any of the five senses. Auditory hallucinations are a common symptom of schizophrenia.

Huntington's chorea—A hereditary disease that typically appears in midlife, marked by gradual loss of brain function and voluntary movement. Some of its symptoms resemble those of schizophrenia.

Negative symptoms—Symptoms of schizophrenia characterized by the absence or elimination of certain behaviors. DSM-IV specifies three negative symptoms: affective flattening, poverty of speech, and loss of will or initiative.

Neuroleptic—Another name for the older type of antipsychotic medications given to schizophrenic patients.

Parkinsonism—A set of symptoms originally associated with Parkinson disease that can occur as side effects of neuroleptic medications. The symptoms include trembling of the fingers or hands, a shuffling gait, and tight or rigid muscles.

Positive symptoms—Symptoms of schizophrenia that are characterized by the production or presence of behaviors that are grossly abnormal or excessive, including hallucinations and thought-process disorder. DSM-IV subdivides positive symptoms into psychotic and disorganized.

Poverty of speech—A negative symptom of schizophrenia, characterized by brief and empty replies to questions. It should not be confused with shyness or reluctance to talk.

Psychotic disorder—A mental disorder characterized by delusions, hallucinations, or other symptoms of lack of contact with reality. The schizophrenias are psychotic disorders.

Serotonin dopamine antagonist (SDA)—The newer second-generation antipsychotic drugs, also called atypical antipsychotics. SDAs include clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa).

Wilson disease—A rare hereditary disease marked by high levels of copper deposits in the brain and liver. It can cause psychiatric symptoms resembling schizophrenia.

Word salad—Speech that is so disorganized that it makes no linguistic or grammatical sense.

functions. Positive symptoms include Schneider's first-rank symptoms as well as disorganized thought processes (reflected mainly in speech) and disorganized or catatonic behavior. Disorganized thought processes are marked by such characteristics as looseness of associations, in which the patient rambles from topic to topic in

a disconnected way; tangentially, which means that the patient gives unrelated answers to questions; and "word salad," in which the patient's speech is so incoherent that it makes no grammatical or linguistic sense. Disorganized behavior means that the patient has difficulty with any type of purposeful or goal-oriented behavior, including personal self-care or preparing meals. Other forms of disorganized behavior may include dressing in odd or inappropriate ways, sexual self-stimulation in public, or agitated shouting or cursing.

Negative symptoms

The *DSM-IV* definition of schizophrenia includes three so-called negative symptoms. They are called negative because they represent the lack or absence of behaviors. The negative symptoms that are considered diagnostic of schizophrenia are a lack of emotional response (affective flattening), poverty of speech, and absence of volition or will. In general, the negative symptoms are more difficult for doctors to evaluate than the positive symptoms.

Diagnosis

A doctor must make a diagnosis of schizophrenia on the basis of a standardized list of outwardly observable symptoms, not on the basis of internal psychological processes. There are no specific laboratory tests that can be used to diagnose schizophrenia. Researchers have, however, discovered that patients with schizophrenia have certain abnormalities in the structure and functioning of the brain compared to normal test subjects. These discoveries have been made with the help of imaging techniques such as computed tomography scans (CT scans).

When a psychiatrist assesses a patient for schizophrenia, he or she will begin by excluding physical conditions that can cause abnormal thinking and some other behaviors associated with schizophrenia. These conditions include organic brain disorders (including traumatic injuries of the brain) temporal lobe **epilepsy**, **Wilson disease**, Huntington's chorea, and encephalitis. The doctor will also need to rule out substance abuse disorders, especially amphetamine use.

After ruling out organic disorders, the clinician will consider other psychiatric conditions that may include psychotic symptoms or symptoms resembling psychosis. These disorders include mood disorders with psychotic features; delusional disorder; dissociative disorder not otherwise specified (DDNOS) or multiple personality disorder; schizotypal, schizoid, or paranoid personality disorders; and atypical reactive disorders. In the past, many individuals were incorrectly diagnosed as schizophrenic. Some patients who were diagnosed prior to the changes in categorization introduced by *DSM-IV* should have their diagnoses, and treatment, reevaluated. In children, the doctor must distinguish between psychotic symptoms and a vivid fantasy life, and also identify learning problems or disorders. After other conditions have been ruled out, the patient must meet a set of criteria specified by *DSM-IV*:

- *Characteristic symptoms*. The patient must have two (or more) of the following symptoms during a one-month period: delusions; hallucinations; disorganized speech; disorganized or catatonic behavior; negative symptoms.
- Decline in social, interpersonal, or occupational functioning, including self-care.
- *Duration*. The disturbed behavior must last for at least six months.
- *Diagnostic exclusions*. Mood disorders, substance abuse disorders, medical conditions, and developmental disorders have been ruled out.

Treatment and management

The treatment of schizophrenia depends in part on the patient's stage or phase. Patients in the acute phase are hospitalized in most cases, to prevent harm to the patient or others and to begin treatment with antipsychotic medications. A patient having a first psychotic episode should be given a CT or MRI (magnetic resonance imaging) scan to rule out structural brain disease.

Antipsychotic medications

The primary form of treatment of schizophrenia is antipsychotic medication. Antipsychotic drugs help to control almost all the positive symptoms of the disorder. They have minimal effects on disorganized behavior and negative symptoms. Between 60-70% of schizophrenics will respond to antipsychotics. In the acute phase of the illness, patients are usually given medications by mouth or by intramuscular injection. After the patient has been stabilized, the antipsychotic drug may be given in a long-acting form called a depot dose. Depot medications last two to four weeks; they have the advantage of protecting the patient against the consequences of forgetting or skipping daily doses. In addition, some patients who do not respond to oral neuroleptics have better results with depot form. Patients whose long-term treatment includes depot medications are introduced to the depot form gradually during their stabilization period. Most people with schizophrenia are kept on antipsychotic medications indefinitely during the maintenance phase of their disorder to minimize the possibility of relapse.

As of 1998, the most frequently used antipsychotics fall into two classes: the older dopamine receptor antag-

onists, or DAs, and the newer serotonin dopamine antagonists, or SDAs. (Antagonists block the action of some other substance; for example, dopamine antagonists counteract the action of dopamine.) The exact mechanisms of action of these medications are not known, but it is thought that they lower the patient's sensitivity to sensory stimuli and so indirectly improve the patient's ability to interact with others.

DOPAMINE RECEPTOR ANTAGONIST The dopamine antagonists include the older antipsychotic (also called neuroleptic) drugs, such as haloperidol (Haldol), chlorpromazine (Thorazine), and fluphenazine (Prolixin). These drugs have two major drawbacks: it is often difficult to find the best dosage level for the individual patient, and a dosage level high enough to control psychotic symptoms frequently produces extrapyramidal side effects, or EPS. EPSs include parkinsonism, in which the patient cannot walk normally and usually develops a tremor; **dystonia**, or painful muscle spasms of the head, tongue, or neck; and akathisia, or restlessness. A type of long-term EPS is called tardive dyskinesia, which features slow, rhythmic, automatic movements. Schizophrenics with AIDS are especially vulnerable to developing EPS.

SERATONIN DOPANINE ANTAGONISTS The serotonin dopamine antagonists, also called atypical antipsychotics, are newer medications that include clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa). The SDAs have a better effect on the negative symptoms of schizophrenia than do the older drugs and are less likely to produce EPS than the older compounds. The newer drugs are significantly more expensive in the short term, although the SDAs may reduce long-term costs by reducing the need for hospitalization. They are also presently unavailable in injectable forms. The SDAs are commonly used to treat patients who respond poorly to the DAs. However, many psychotherapists now regard the use of these atypical antipsychotics as the treatment of first choice.

Psychotherapy

Most schizophrenics can benefit from psychotherapy once their acute symptoms have been brought under control by antipsychotic medication. Psychoanalytic approaches are not recommended. Behavior therapy, however, is often helpful in assisting patients to acquire skills for daily living and social interaction. It can be combined with occupational therapy to prepare the patient for eventual employment.

Family therapy

Family therapy is often recommended for the families of schizophrenic patients, to relieve the feelings of guilt that they often have as well as to help them understand the patient's disorder. The family's attitude and behaviors toward the patient are key factors in minimizing relapses (for example, by reducing stress in the patient's life), and family therapy can often strengthen the family's ability to cope with the stresses caused by the schizophrenic's illness. Family therapy focused on communication skills and problem-solving strategies is particularly helpful. In addition to formal treatment, many families benefit from support groups and similar mutual help organizations for relatives of schizophrenics.

Prognosis

One important prognostic sign is the patient's age at onset of psychotic symptoms. Patients with early onset of schizophrenia are more often male, have a lower level of functioning prior to onset, a higher rate of brain abnormalities, more noticeable negative symptoms, and worse outcomes. Patients with later onset are more likely to be female, with fewer brain abnormalities and thought impairment, and more hopeful prognoses.

The average course and outcome for schizophrenics are less favorable than those for most other mental disorders, although as many as 30% of patients diagnosed with schizophrenia recover completely and the majority experience some improvement. Two factors that influence outcomes are stressful life events and a hostile or emotionally intense family environment. Schizophrenics with a high number of stressful changes in their lives, or who have frequent contacts with critical or emotionally overinvolved family members, are more likely to relapse. Overall, the most important component of long-term care of schizophrenic patients is complying with their regimen of antipsychotic medications.

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Laith Farid Gulli, MD

Schwartz-Jampel syndrome

Definition

Schwartz-Jampel syndrome (SJS) is a rare, inherited condition of the skeletal and muscle systems that causes short stature, joint limitations, and particular facial features.

Description

First described in 1962, SJS is now a clearly defined syndrome that is divided into two types. Type 1A is the classical form that develops in early childhood, usually between the first and third year of life. Type 1B is less common but more severe and its symptoms are present at birth. Both types of SJS involve generalized disease of the muscles called myopathy. The muscles tend to be quite stiff and are unable to relax normally. This is a condition known as myotonia. The myotonia causes many joints in the body to stay in a bent or flexed position (joint contractures).

In addition to muscle problems, the bones in the skeleton do not develop normally and this is why SJS may also be called a type of skeletal **dysplasia**. Abnormal bone shape and poor bone growth result in decreased total height, incorrect arm and leg postures, as well as curving of the spine (**scoliosis**).

Unique facial features of SJS include narrow eye openings with drooping eye lids, a small mouth, and puckered lips. These features are also due to the stiffness of the muscles that support the face and individuals with SJS appear to have a fixed facial expression.

Persons affected with SJS often have normal intelligence, although varying degrees of mental retardation may affect as many as 25% of patients. However, the myotonia may lead to poor speech articulation and drooling so that affected individuals are sometimes misdiagnosed as having mental retardation.

Respiratory and feeding difficulties are frequent with SJS Type 1B due to the more severe nature of the muscle and bone disease. These problems may be fatal in early infancy. Persons with SJS Type 1A have a much longer life expectancy, although this depends on how their disease progresses.

SJS has also been referred to as:

- myotonic myopathy, dwarfism, chrondrodystrophy, and ocular and facial abnormalities
- Schwartz-Jampel-Aberfeld syndrome
- Schwartz syndrome
- Aberfeld syndrome
- chrondrodystrophic myotonia
- osteochondromuscular dystrophy
- spondylo-epimetaphyseal dysplasia with myotonia

Genetic profile

Both types of SJS are known to be inherited in an autosomal recessive manner. This was concluded after the following observations were made. SJS affects males and females alike. Parents of affected individuals rarely show any signs or symptoms of SJS. Parents have been reported to have more than one affected child. Consanguineous relationships were seen in some families.

Genetic studies of many families revealed that all cases of SJS were linked to an area on chromosome one, described as 1p36.1. A **gene** in this region, named

HSPG2, makes a protein called perlecan that is thought to play the primary role in causing SJS. The function of the perlecan protein is not completely understood. However, it has an important job in the cells of the body's connective tissue (bone, cartilage, muscles, ligaments, tendons and blood vessels). As of the year 2001, studies have shown that perlecan helps keep cartilage and bone strong and are essential for certain chemical processes in the muscle tissue. It is also thought that perlecan helps to direct the normal growth of some cells.

The gene for perlecan (HSPG2) is fairly large and mistakes or mutations in the instructions of the gene have been found in some persons with SJS. These gene mutations change how the perlecan protein is made and usually prevents it from doing its normal job in the muscles and bones of the body. The effects of these HSPG2 gene mutations cause SJS.

The location 1p36.1 means that the gene is near the top or end of the short arm of chromosome number one. A human being has 23 pairs of **chromosomes** in nearly every cell of their body. One of each kind (23 total) is inherited from the mother and another of each kind (23 total) is inherited from the father, for a total of 46. One chromosome may hold hundreds to thousands of individual genes and as the chromosomes exist in pairs, so do the genes. Therefore, every person has two copies of the HSPG2 gene that makes perlecan. Individuals that have a diagnosis of SJS are thought to have a mutation in both copies of their HSPG2 gene, each of which was inherited from one of their parents. Unaffected parents of children with SJS are therefore carriers for SJS. Their one normal HSPG2 gene appears to make enough perlecan so those carriers do not show any symptoms of SJS. Most parents do not know that they are carriers for SJS until they have an affected child. When both parents are carriers for the same autosomal recessive disease such as SJS, there is a 25% chance with each and every pregnancy that they have together that their child will inherit both mutated HSPG2 genes and develop SJS.

Demographics

SJS is a very rare genetic syndrome that affects males and females in many ethnic backgrounds. The exact incidence is unknown. Approximately 100 cases have been reported in scientific publications as of the year 2001. This may not accurately reflect the incidence of SJS, as some persons may not come to medical attention or may be misdiagnosed.

Signs and symptoms

A child born with SJS Type 1A may show no outward signs of the condition at birth. Over the following one to three years, progressive myotonia of the muscles and resulting joint contractures develop. The typical bone problems become obvious and growth in height slows down. These symptoms are evident at birth in children with SJS Type 1B. The following descriptions apply to both SJS Type 1A and Type 1B. However, each person with SJS may be affected to a different degree and their kinds of symptoms may vary.

KEY TERMS

Blepharophimosis—A small eye opening without fusion of the upper eyelid with the lower eyelid at the inner and outer corner of the eye.

Consanguineous—Sharing a common bloodline or ancestor.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Myopathy—Any abnormal condition or disease of the muscle.

Myotonia—The inability to normally relax a muscle after contracting or tightening it.

Head and neck

Myotonia of the muscles in the face causes a tight and fixed facial expression. The eye openings are almost always narrowed and small and the upper and lower eyelids are not joined properly at the corners of the eye (blepharophimosis). The upper eyelid may also appear droopy (ptosis). Nearsightedness (**myopia**) is present in 50% of patients and occasionally cataracts and lens dislocation may develop in the eye. The mouth is small and lips are puckered due to tight facial muscles. This may lead to speech difficulty. The chin may also be small or set back.

Body

Hernias of the groin and navel areas are often noticed at birth. A hernia is the bulging of a tissue outside of its normal space and a simple operation can usually place it back inside. *Pectus carinatum* is a common bony deformity of the chest that causes the breast bone to protrude forward. Abnormalities in the growth and development of the bones of the spinal column (vertebrae) lead to scoliosis that usually worsens with age. Development of puberty is most often normal for persons with SJS.

Limbs

Some babies with SJS are born with a dislocation of their hip joint. This is common in infants without SJS as

well. As the muscle disease of SJS progresses, the joints become very stiff. The hips, knees, and elbows in particular have very limited range of motion. These joint contractures worsen until puberty and then tend to stay the same from that point on. Eventually, a wheelchair is needed due to significant limitation of movement. The long bones in the body (i.e.: the thighbone) are bowed and shortened. This can cause a person with SJS to waddle as they walk and to stand in a crouching position. Therefore, an individual with SJS tends to be shorter than 90% of unaffected persons their age. A few have been reported to reach average height. Typically, their arms and legs have an increased amount of body hair as well.

Muscles

The muscles of the body show progressive myotonia, as they remain tight and are unable to relax normally. The muscle bulk may be increased in some areas, such as the thighs, and may waste away in others. As the muscles are unable to function normally, physical activity is restricted and a person may tire very easily.

Central nervous system and behavior

Most individuals with SJS have normal intelligence, although some degree of mental retardation has been reported. Developmental language problems and attention difficulties have also been seen in some cases. Reflexes tend to be slower than normal. A high-pitched voice and drooling may be noticed due to muscle stiffness in the mouth and throat area. This may cause feeding difficulties and choking may be of concern.

Diagnosis

The diagnosis of SJS Type 1A or Type 1B is made mainly by the presence of the symptoms described above. There is no specific biochemical or muscle testing that confirms a suspected diagnosis. Although research studies have identified mutations in the HSPG2 gene in some families, widespread **genetic testing** is not clinically available as of the year 2001. Such genetic mutations may be unique to each family and therefore may not be found in other persons affected with SJS.

Several different studies may be performed to determine the type and severity of muscle disease when considering a diagnosis of SJS. This may include a muscle biopsy that samples a piece of muscle and examines the appearance of the muscle cells. A muscle biopsy may appear normal or it may show signs of myopathy. A particular chemical, called creatine kinase, can be measured in a person's blood. Very high levels of creatine kinase usually indicate the presence of muscle disease or wasting. An electromyogram (EMG) is a test that measures the electrical currents made within an active muscle. The EMG pattern is usually abnormal in persons with SJS. These tests will confirm the presence of muscle disease but there are no specific changes in any of them that are unique to SJS.

The following are some abnormalities of the bones that are frequently noticed on x rays:

- flat and irregularly formed vertebrae
- deformity of the upper part of the thigh bone
- a flattened joint socket where the hip and thigh bone meet
- specific changes in the development of the bones in the hand
- bowing of the long bones, especially the leg bones
- curvature of the spine that causes a hunchback appearance

Many of the symptoms of SJS are also present in other conditions and it is important to distinguish SJS from the following disorders:

- **Stuve-Wiedemann syndrome** (which was previously called SJS Type 2 until it was determined that they were the same condition)
- Freeman-Sheldon syndrome (also known as whistling face syndrome)
- Marden-Walker syndrome
- Kniest dysplasia
- **Seckel syndrome**
- **myotonic dystrophy**
- the mucopolysaccharidoses

Treatment and management

There is not a cure for SJS. The treatment involves managing the symptoms of the condition as they develop and supporting the needs of the individual as the disability progresses. Several medical specialists may monitor a person with SJS for particular symptoms or complications. An orthopedic doctor manages the abnormal bone development and may offer surgical options for treatment of hip dislocation, scoliosis, or bone curvature. An ophthalmologist monitors eye problems such as nearsightedness and cataracts, for which glasses and surgery may be available. Cosmetic repair of blepharophimosis by plastic surgery may also be considered.

For those with a mental deficiency, special education programs with options for activities in regular classrooms may offer the best opportunities for learning. Physical therapy may help maintain the greatest possible range of motion of the joints and speech therapy may improve

speech problems due to a small and tight mouth. Physical activities of children are usually limited due to their stiff joints. As the condition progresses, persons with SJS are often wheelchair-bound by their teenage years and occupational therapy may help improve their everyday living skills. Adults who live independently may require some assistance with everyday tasks that their disability prevents them from doing, such as household chores or even bathing.

Prognosis

Individuals with SJS can live well into adulthood despite progressive disability but the average life expectancy is unclear. They are usually wheelchair-bound by their teenage or young adult years. Although puberty development may be normal, no reports have been made of an individual with SJS fathering children or carrying a pregnancy.

SJS Type 1B may be fatal in the newborn period due to serious respiratory and feeding problems. As the muscles in the face and neck may be very tight, it can be difficult to place a tube down the throat (intubation) to allow a baby to breathe. Feeding may be a continuous struggle due to problems with or an inability to swallow.

Both types of SJS cause persons to be more prone to develop chest infections and pneumonia. There is also an increased risk for complications from anesthesia, specifically **malignant hyperthermia** (MH). MH is an abnormal chemical reaction in the body to the use of some anesthesia medications. It causes high fevers, breathing difficulty, rigid muscles and general serious illness. This condition may be life threatening.

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National Eye Institute. 31 Center Drive, Bldg. 31, Room6A32, MSC 2510, Bethseda, MD 20892-2510. (301) 496-5248. 2020@nei.nih.gov. <http://www.nei.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Jennifer Elizabeth Neil, MS, CGC

SCIDX *see* **Severe combined immunodeficiency, X-linked**

Sclerocornea *see* **Microphthalmia with linear skin defects**

Scleroderma

Definition

Scleroderma is a progressive disease that affects the skin and connective tissue (including cartilage, bone, fat, and the tissue that supports the nerves and blood vessels throughout the body). There are two major forms of the disorder. The type known as localized scleroderma mainly affects the skin. Systemic scleroderma, which is also called systemic sclerosis, affects the smaller blood vessels and internal organs of the body.

Description

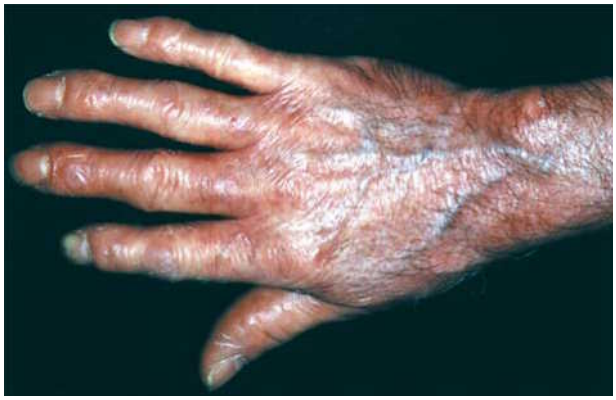
Scleroderma is an autoimmune disorder, which means that the body's immune system turns against itself. In scleroderma, there is an overproduction of abnormal collagen (a type of protein fiber present in connective tissue). This collagen accumulates throughout the body, causing hardening (sclerosis), scarring (fibrosis), and other damage. The damage may affect the appearance of the skin, or it may involve only the internal organs. The symptoms and severity of scleroderma vary from person to person.

Genetic profile

The role of genetics in the transmission in scleroderma is unclear. Some cases clearly run in families, but most occur in people without any family history of the disease.

Demographics

Scleroderma occurs in all races of people all over the world, but it affects about four females for every male. Among children, localized scleroderma is more common,



Scleroderma results in thickening and toughening of the skin, which may also become inflamed. *(Photo Researchers, Inc.)*

and systemic sclerosis is comparatively rare. Most patients with systemic sclerosis are diagnosed between ages 30 and 50. In the United States, about 300,000 people have scleroderma. Young African American women and Native Americans of the Choctaw tribe have especially high rates of the disease.

Signs and symptoms

The cause of scleroderma is still uncertain. Although the accumulation of collagen appears to be a hallmark of the disease, researchers do not know why it occurs. Some theories suggest that damage to blood vessels may cause the tissues of the body to receive an inadequate amount of oxygen—a condition called ischemia. Some researchers believe that the resulting damage causes the immune system to overreact, producing an autoimmune disorder. According to this theory of scleroderma, the immune system gears up to fight an invader, but no invader is actually present. Cells in the immune system, called antibodies, react to the body's own tissues as if they were foreign. The antibodies turn against the already damaged blood vessels and the vessels' supporting tissues. These immune cells are designed to deliver potent chemicals in order to kill foreign invaders. Some of these cells dump these chemicals on the body's own tissues instead, causing inflammation, swelling, damage, and scarring.

Most cases of scleroderma have no recognizable triggering event. Some cases, however, have been traced to exposure to toxic (poisonous) substances. For example, coal miners and gold miners, who are exposed to high levels of silica dust, have above-average rates of scleroderma. Other chemicals associated with the disease include polyvinyl chloride, benzine, toluene, and epoxy resins. In 1981, 20,000 people in Spain were stricken with a syndrome similar to scleroderma when their cooking oil was accidentally contaminated. Certain medications, especially a drug used in **cancer** treatment called bleomycin (Blenoxane), may lead to scleroderma. Some claims of a scleroderma-like illness have been made by women with silicone breast implants, but a link has not been proven in numerous studies.

Symptoms of systemic scleroderma

A condition called Raynaud's phenomenon is the first symptom in about 95% of all patients with systemic scleroderma. In Raynaud's phenomenon, the blood vessels of the fingers and/or toes (the digits) react to cold in an abnormal way. The vessels clamp down, preventing blood flow to the tip of the digit. Eventually, the flow is cut off to the entire finger or toe. Over time, oxygen deprivation may result in open ulcers on the skin surface. These ulcers can lead to tissue death (gangrene) and loss of the digit. When Raynaud's phenomenon is the first sign of scleroderma, the next symptoms usually appear within two years.

SKIN AND EXTREMITIES Involvement of the skin leads to swelling underneath the skin of the hands, feet, legs, arms, and face. Swelling is followed by thickening and tightening of the skin, which becomes taut and shiny. Severe tightening may lead to abnormalities. For example, tightening of the skin on the hands may cause the fingers to become permanently curled (flexed). Structures within the skin are damaged (including those producing hair, oil, and sweat), and the skin becomes dry and scaly. Ulcers may form, with the danger of infection. Calcium deposits often appear under the skin.

In systemic scleroderma, the mouth and nose may become smaller as the skin on the face tightens. The small mouth may interfere with eating and dental hygiene. Blood vessels under the skin may become enlarged and show through the skin, appearing as purplish marks or red spots. This chronic dilation of the small blood vessels is called telangiectasis.

Muscle weakness, joint pain and stiffness, and carpal tunnel syndrome are common in scleroderma. Carpal tunnel syndrome involves scarring in the wrist, which puts pressure on the median nerve running through that area. Pressure on the nerve causes numbness, tingling, and weakness in some of the fingers.

DIGESTIVE TRACT The tube leading from the mouth to the stomach (the esophagus) becomes stiff and scarred. Patients may have trouble swallowing food. The acid contents of the stomach may start to flow backward into the esophagus (esophageal reflux), causing a very uncomfortable condition known as heartburn. The esophagus may also become inflamed.

The intestine becomes sluggish in processing food, causing bloating and pain. Foods are not digested properly, resulting in diarrhea, weight loss, and anemia. Telangiectasis in the stomach or intestine may cause rupture and bleeding.

RESPIRATORY AND CIRCULATORY SYSTEMS The lungs are affected in about 66% of all people with systemic scleroderma. Complications include shortness of breath, coughing, difficulty breathing due to tightening of the tissue around the chest, inflammation of the air sacs in the lungs (alveolitis), increased risk of pneumonia, and an increased risk of cancer. For these reasons, lung disease is the most likely cause of death associated with scleroderma.

The lining around the heart (pericardium) may become inflamed. The heart may have greater difficulty pumping blood effectively (heart failure). Irregular heart rhythms and enlargement of the heart also occur in scleroderma.

Kidney disease is another common complication. Damage to blood vessels in the kidneys often causes a major rise in the person's blood pressure. The blood pressure may be so high that there is swelling of the brain, causing severe headaches, damage to the retinas of the eyes, seizures, and failure of the heart to pump blood into the body's circulatory system. The kidneys may also stop filtering blood and go into failure. Treatments for high blood pressure have greatly improved these kidney complications. Before these treatments were available, kidney problems were the most common cause of death for people with scleroderma.

Other problems associated with scleroderma include painful dryness of the eyes and mouth, enlargement and destruction of the liver, and a low-functioning thyroid gland.

Diagnosis

Diagnosis of scleroderma is complicated by the fact that some of its symptoms can accompany other connective-tissue diseases. The most important symptom is thickened or hardened skin on the fingers, hands, forearms, or face. This is found in 98% of people with scleroderma. It can be detected in the course of a physical examination. The person's medical history may also contain important clues, such as exposure to toxic substances on the job. There are a number of nonspecific laboratory tests on blood samples that may indicate the presence of an inflammatory disorder (but not specifically scleroderma). The antinuclear antibody (ANA) test is positive in more than 95% of people with scleroderma.

Other tests can be performed to evaluate the extent of the disease. These include a test of the electrical system of the heart (an electrocardiogram), lung-function tests, and x ray studies of the gastrointestinal tract. Various blood tests can be given to study kidney function.

KEY TERMS

Autoimmune disorder—A disorder in which the body's immune cells mistake the body's own tissues as foreign invaders; the immune cells then work to destroy tissues in the body.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Fibrosis—The abnormal development of fibrous tissue; scarring.

Limited scleroderma—A subtype of systemic scleroderma with limited skin involvement. It is sometimes called the CREST form of scleroderma, after the initials of its five major symptoms.

Localized scleroderma—Thickening of the skin from overproduction of collagen.

Morphea—The most common form of localized scleroderma.

Raynaud phenomenon/Raynaud disease—A condition in which blood flow to the body's tissues is reduced by a malfunction of the nerves that regulate the constriction of blood vessels. When attacks of Raynaud's occur in the absence of other medical conditions, it is called Raynaud disease. When attacks occur as part of a disease (as in scleroderma), it is called Raynaud phenomenon.

Sclerosis—Hardening.

Systemic sclerosis—A rare disorder that causes thickening and scarring of multiple organ systems.

Telangiectasis—Very small arteriovenous malformations, or connections between the arteries and veins. The result is small red spots on the skin known as "spider veins".

Treatment and management

At this time there is no cure for scleroderma. A drug called D-penicillamine has been used to interfere with the abnormal collagen. It is believed to help decrease the degree of skin thickening and tightening, and to slow the

progress of the disease in other organs. Taking vitamin D and using ultraviolet light may be helpful in treating localized scleroderma. Corticosteroids have been used to treat joint pain, muscle cramps, and other symptoms of inflammation. Other drugs have been studied that reduce the activity of the immune system (immunosuppressants). Because these medications can have serious side effects, they are used in only the most severe cases of scleroderma.

The various complications of scleroderma are treated individually. Raynaud's phenomenon requires that people try to keep their hands and feet warm constantly. Nifedipine is a medication that is sometimes given to help control Raynaud's. Thick ointments and creams are used to treat dry skin. Exercise and massage may help joint involvement; they may also help people retain more movement despite skin tightening. Skin ulcers need prompt attention and may require antibiotics. People with esophageal reflux will be advised to eat small amounts more often, rather than several large meals a day. They should also avoid spicy foods and items containing caffeine. Some patients with esophageal reflux have been successfully treated with surgery. Acid-reducing medications may be given for heartburn. People must be monitored for the development of high blood pressure. If found, they should be promptly treated with appropriate medications, usually ACE inhibitors or other vasodilators. When fluid accumulates due to heart failure, diuretics can be given to get rid of the excess fluid.

Prognosis

The prognosis for people with scleroderma varies. Some have a very limited form of the disease called morphea, which affects only the skin. These individuals have a very good prognosis. Other people have a subtype of systemic scleroderma called limited scleroderma. For them, the prognosis is relatively good. Limited scleroderma is characterized by limited involvement of the patient's skin and a cluster of five symptoms called the CREST syndrome. CREST stands for:

- C = Calcinosis
- R = Raynaud's disease (phenomenon)
- E = Esophageal dysmotility (stiffness and malfunctioning of the esophagus)
- S = Sclerodactyly (thick, hard, rigid skin over the fingers)
- T = Telangiectasis

In general, people with very widespread skin involvement have the worst prognosis. This level of disease is usually accompanied by involvement of other organs and the most severe complications. Although women are more commonly stricken with scleroderma, men more often die of the disease. The most common causes of death include heart, kidney, and lung diseases. About 65% of all patients survive 10 years or more following a diagnosis of scleroderma.

There are no known ways to prevent scleroderma. People can try to decrease occupational exposure to high-risk substances.

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American College of Rheumatology. 60 Executive Park South, Suite 150, Atlanta, GA 30329. (404) 633-3777. <http://www.rheumatology.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Scleroderma Foundation. 12 Kent Way, Suite 101, Byfield, MA 01922. (978) 463-5843 or (800) 722-HOPE. Fax: (978) 463-5809. <http://www.scleroderma.org.>.

Rebecca J. Frey, PhD

Scoliosis

Definition

Scoliosis is a side-to-side curvature of the spine of 10 degrees or greater.

Description

When viewed from the rear, the spine usually appears to form a straight vertical line. Scoliosis is a lateral (side-to-side) curve in the spine, usually combined with a rotation of the vertebrae. (The lateral curvature of scoliosis should not be confused with the normal set of front-to-back spinal curves visible from the side.) While a small degree of lateral curvature does not cause any medical problems, larger curves can cause postural imbalance and lead to muscle fatigue and pain. More severe scoliosis can interfere with breathing and lead to arthritis of the spine (spondylosis).

Four out of five cases of scoliosis are *idiopathic*, meaning the cause is unknown. Children with idiopathic scoliosis appear to be otherwise entirely healthy, and have not had any bone or joint disease early in life. Scoliosis is not caused by poor posture, diet, or carrying a heavy bookbag exclusively on one shoulder.

Idiopathic scoliosis is further classified according to age of onset:

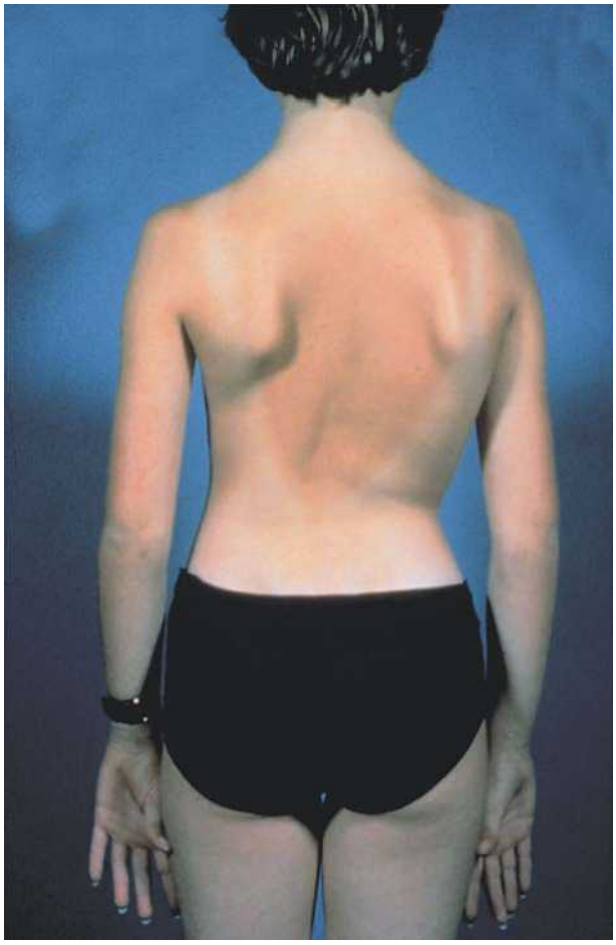
- Infantile. Curvature appears before age three. This type is quite rare in the United States, but is more common in Europe.
- Juvenile. Curvature appears between ages three and 10. This type may be equivalent to the adolescent type, except for the age of onset.
- Adolescent. Curvature appears between ages of 10 and 13, near the beginning of puberty. This is the most common type of idiopathic scoliosis.
- Adult. Curvature begins after physical maturation is completed.

Causes are known for three other types of scoliosis:

- Congenital scoliosis is due to congenital birth defects in the spine, often associated with other structural abnormalities.
- Neuromuscular scoliosis is due to loss of control of the nerves or muscles that support the spine. The most common causes of this type of scoliosis are **cerebral palsy** and muscular dystrophy.
- Degenerative scoliosis may be caused by degeneration of the discs that separate the vertebrae or arthritis in the joints that link them.

Genetic profile

Idiopathic scoliosis has long been observed to run in families. Twin and family studies have consistently indicated a genetic contribution to the condition. However, no consistent pattern of transmission has been observed in familial cases. As of 2000, no genes have been identified which specifically cause or predispose to the idiopathic form of scoliosis.



A woman with idiopathic scoliosis. *(Custom Medical Stock Photo, Inc.)*

There are several genetic syndromes that involve a predispostion to scoliosis, and several studies have investigated whether or not the genes causing these syndromes may also be responsible for idiopathic scoliosis. Using this *candidate gene approach*, the genes responsible for **Marfan syndrome** (fibrillin), **Stickler syndrome**, and some forms of **osteogenesis imperfecta** (collagen types I and II) have not been shown to correlate with idiopathic scoliosis.

Attempts to map a **gene** or genes for scoliosis have not shown consistent linkage to a particular chromosome region.

Most researchers have concluded that scoliosis is a complex trait. As such, there are likely to be multiple genetic, environmental, and potentially additional factors that contribute to the etiology of the condition. Complex traits are difficult to study due to the difficulty in identifying and isolating these multiple factors.

KEY TERMS

Cobb angle—A measure of the curvature of scoliosis, determined by measurements made on x rays.

Scoliometer—A tool for measuring trunk asymmetry; it includes a bubble level and angle measure.

Spondylosis—Arthritis of the spine.

Demographics

The incidence of scoliosis in the general population is 2-3%. Among adolecents, however, 10% have some degree of scoliosis (though fewer than 1% have curves which require treatment).

Scoliosis is found in both boys and girls, but a girl's spinal curve is much more likely to progress than a boy's. Girls require scoliosis treatment about five times as often. The reason for these differences is not known, but may relate to increased levels of estrogen and other hormones.

Signs and symptoms

Scoliosis causes a noticeable asymmetry in the torso when viewed from the front or back. The first sign of scoliosis is often seen when a child is wearing a bathing suit or underwear. A child may appear to be standing with one shoulder higher than the other, or to have a tilt in the waistline. One shoulder blade may appear more prominent than the other due to rotation. In girls, one breast may appear higher than the other, or larger if rotation pushes that side forward.

Curve progression is greatest near the adolescent growth spurt. Scoliosis that begins early on is more likely to progress significantly than scoliosis that begins later in puberty.

More than 30 states have screening programs in schools for adolescent scoliosis, usually conducted by trained school nurses or gym teachers.

Diagnosis

Diagnosis for scoliosis is done by an orthopedist. A complete medical history is taken, including questions about family history of scoliosis. The physical examination includes determination of pubertal development in adolescents, a neurological exam (which may reveal a neuromuscular cause), and measurements of trunk asymmetry. Examination of the trunk is done while the patient is standing, bending over, and lying down, and involves both visual inspection and use of a simple mechanical device called a scoliometer.

If a curve is detected, one or more x rays will usually be taken to define the curve or curves more precisely. An x ray is used to document spinal maturity, any pelvic tilt or hip asymmetry, and the location, extent, and degree of curvature. The curve is defined in terms of where it begins and ends, in which direction it bends, and by an angle measure known as the Cobb angle. The Cobb angle is found by projecting lines parallel to the vertebrae tops at the extremes of the curve; projecting perpendiculars from these lines; and measuring the angle of intersection. To properly track the progress of scoliosis, it is important to project from the same points of the spine each time.

Occasionally, magnetic resonance imaging (MRI) is used, primarily to look more closely at the condition of the spinal cord and nerve roots extending from it if neurological problems are suspected.

Treatment and management

Treatment decisions for scoliosis are based on the degree of curvature, the likelihood of significant progression, and the presence of pain, if any.

Curves less than 20 degrees are not usually treated, except by regular follow-up for children who are still growing. Watchful waiting is usually all that is required in adolescents with curves of 20-25 degrees, or adults with curves up to 40 degrees or slightly more, as long as there is no pain.

For children or adolescents whose curves progress to 25 degrees, and who have a year or more of growth left, bracing may be required. Bracing cannot correct curvature, but may be effective in halting or slowing progression. Bracing is rarely used in adults, except where pain is significant and surgery is not an option, as in some elderly patients.

There are two different categories of braces, those designed for nearly 24 hour per day use and those designed for night use. The full-time brace styles are designed to hold the spine in a vertical position, while the night use braces are designed to bend the spine in the direction opposite the curve.

The Milwaukee brace is a full-time brace which consists of metal uprights attached to pads at the hips, rib cage, and neck. Other types of full-time braces, such as the Boston brace, involve underarm rigid plastic molding to encircle the lower rib cage, abdomen, and hips. Because they can be worn out of sight beneath clothing, the underarm braces are better tolerated and often leads to better compliance. The Boston brace is currently the

most commonly used. Full-time braces are often prescribed to be worn for 22-23 hours per day, though some clinicians believe that recommending brace use of 16 hours leads to better compliance and results.

Night use braces bend the patient's scoliosis into a correct angle, and are prescribed for 8 hours of use during sleep. Some investigators have found that night use braces are not as effective as the day use types.

Bracing may be appropriate for scoliosis due to some types of neuromuscular disease, including **spinal muscular atrophy**, before growth is finished. **Duchenne muscular dystrophy** is not treated by bracing, since surgery is likely to be required, and since later surgery is complicated by loss of respiratory capacity.

Surgery for idiopathic scoliosis is usually recommended if:

- the curve has progressed despite bracing
- the curve is greater than 40-50 degrees before growth has stopped in an adolescent
- the curve is greater than 50 degrees and continues to increase in an adult
- there is significant pain

Orthopedic surgery for neuromuscular scoliosis is often done earlier. The goals of surgery are to correct the deformity as much as possible, to prevent further deformity, and to eliminate pain as much as possible. Surgery can usually correct 40-50% of the curve, and sometimes as much as 80%. Surgery cannot always completely remove pain.

The surgical procedure for scoliosis is called *spinal fusion*, because the goal is to straighten the spine as much as possible, and then to fuse the vertebrae together to prevent further curvature. To achieve fusion, the involved vertebra are first exposed, and then scraped to promote regrowth. Bone chips are usually used to splint together the vertebrae to increase the likelihood of fusion. To maintain the proper spinal posture before fusion occurs, metal rods are inserted alongside the spine, and are attached to the vertebrae by hooks, screws, or wires. Fusion of the spine makes it rigid and resistant to further curvature. The metal rods are no longer needed once fusion is complete, but are rarely removed unless their presence leads to complications.

Spinal fusion leaves the involved portion of the spine permanently stiff and inflexible. While this leads to some loss of normal motion, most functional activities are not strongly affected, unless the very lowest portion of the spine (the lumbar region) is fused. Normal mobility, exercise, and even contact sports are usually all possible after spinal fusion. Full recovery takes approximately six months.

Prognosis

The prognosis for a person with scoliosis depends on many factors, including the age at which scoliosis begins and the treatment received. Most cases of mild adolescent idiopathic scoliosis need no treatment, do not progress, and do not cause pain or functional limitations. Untreated severe scoliosis often leads to spondylosis, and may impair breathing.

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ORGANIZATION

National Scoliosis Foundation. 5 Cabot Place, Stoughton, MA 02072 (781)-341-6333.

Jennifer Roggenbuck, MS,CGC

Sebastian platelet syndrome *see* **Sebastian syndrome**

Sebastian syndrome

Definition

Sebastian syndrome is an extremely rare genetic disease that results in impaired blood clotting function and abnormal platelet formation. Another name for Sebastian syndrome is autosomal dominant macrothrombocytopenia with leukocyte inclusions.

Description

Sebastian syndrome is classified as one of the inherited giant platelet disorders (IGPDs). Platelet cells are components of the blood that play a key role in blood clotting. All IGPDs are associated with bleeding disorders due to improper platelet function and increased platelet cell size. Other IGPDs include May-Hegglin anomaly, Epstein syndrome, Fechtner syndrome, and Bernard-Soulier syndrome. Sebastian syndrome is distinguished from these other IGPDs by subtle differences in the platelet and white blood cell structure and by the lack of symptoms other than bleeding abnormalities.

People affected by Sebastian syndrome have mild, non-life-threatening dysfunction of the blood related to

KEY TERMS

Inherited giant platelet disorder (IGPD)—A group of hereditary conditions that cause abnormal blood clotting and other conditions.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

decreased blood clotting function. They may bruise easily or be prone to nosebleeds.

Genetic profile

Sebastian syndrome is inherited as an autosomal dominant trait. Autosomal means that the syndrome is not carried on a sex chromosome, while dominant means that only one parent has to pass on the **gene mutation** in order for the child to be affected with the syndrome.

Genetic studies in the year 2000 proved that Sebastian syndrome is due to a mutation in the **gene** that encodes a specific enzyme known as nonmuscle myosin heavy chain 9 (the MYH9 gene). The gene locus is 22q11.2, or, the eleventh band of the q arm of chromosome 22. Research has also shown that mutations in the same gene are responsible for May-Hegglin anomaly and Fechtner syndrome, two other inherited giant platelet disorders.

Demographics

Sebastian syndrome is extremely rare and less than 10 affected families have been reported in the medical literature. Due to the very small number of cases, demographic trends for the disease have not been established. Affected individuals have been identified in Caucasian, Japanese, African-American, Spanish, and Saudi Arabian families, so there does not seem to be any clear ethnic pattern to the disease. Both males and females appear to be affected with the same probability.

Signs and symptoms

The symptoms of Sebastian syndrome include a propensity for nosebleeds, bleeding from the gums, mildly increased bleeding time after being cut, and a tendency to bruise easily. Women may experience heavier than normal menstrual bleeding. People with Sebastian syndrome may experience severe hemorrhage after undergoing surgery for any reason. Some individuals with Sebastian syndrome may not have any observable physical signs of the disorder at all.

Diagnosis

Diagnostic blood tests to confirm the decreased blood clotting function seen in Sebastian syndrome may include a complete blood count (CBC) to determine the number of platelets in a blood sample; blood coagulation studies; or platelet aggregation tests.

There are several other disorders, including nongenetic diseases, that can cause symptoms similar to those seen in Sebastian syndrome. A family history of easy bleeding or bruising is an important clue in diagnosing Sebastian syndrome. Once the hereditary nature of the disease is confirmed, establishing a dominant **inheritance** pattern can separate Sebastian syndrome from other inherited giant platelet disorders.

Microscopic studies of the blood can reveal the enlarged platelets and the specific shape and structure characteristics associated with Sebastian syndrome. These characteristics include a shape that is less disc-like than normal platelets. There are also bluish inclusions, or small foreign bodies, observed in the white blood cells.

Genetic sequencing to confirm the presence of a mutation on the MYH9 gene is another method to positively diagnose Sebastian syndrome, although this would rarely be performed in lieu of other methods.

Treatment and management

No treatment is required for the majority of people affected with Sebastian syndrome. After surgery, platelet transfusion may be required in order to avoid the possibility of hemorrhage. People diagnosed with Sebastian syndrome should be made aware of the risks associated with excessive bleeding.

Prognosis

People with Sebastian syndrome can be expected to have a normal lifespan. The main risk for some patients is the chance of severe bleeding after surgery or injury.

Resources

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National Heart, Lung, and Blood Institute. PO Box 30105, Bethesda, MD 20824-0105. (301) 592-8573. nhlbiinfo@rover.nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paul A. Johnson

Seckel syndrome

Definition

Seckel syndrome is an extremely rare inherited disorder characterized by low birth weight, dwarfism, a very small head, mental retardation, and unusual characteristic facial features, including a "beak-like" protrusion of the nose, large eyes, a narrow face, low ears, and an unusually small jaw. Common signs also include abnormalities of bones in the arms and legs.

Description

Seckel syndrome is one of the microcephalic primordial dwarfism syndromes—a category of disorders characterized by profound growth delay. It is marked by dwarfism, a small head, developmental delay, and mental retardation. Abnormalities may also be found in the cardiovascular, hematopoietic, endocrine, and central nervous systems. Children with the disorder are often hyperactive and easily distracted; about half have IQs below 50. Individuals with Seckel syndrome are able to live for an extended period of time.

Seckel syndrome is also known as "bird-headed dwarfism," Seckel type dwarfism, and nanocephalic dwarfism. The disorder was named after Helmut G.P. Seckel, a German pediatrician who came to the United States in 1936. Dr. Seckel did not discover the syndrome but he authored a publication describing the disorder's symptoms based on two of his patients.

Genetic profile

Seckel syndrome displays an autosomal-recessive pattern of **inheritance**. This means that both parents of a child with the disorder carry a copy of the Seckel gene—but the parents appear entirely normal. When both parents carry a copy of the Seckel **gene**, their children face a one in four chance of developing the disorder.

KEY TERMS

Microcephalic primordial dwarfism syndromes—A group of disorders characterized by profound growth delay and small head size.

Demographics

Seckel syndrome is extremely rare. Between 1960—the year that Dr. Seckel defined the disorder—and 1999, fewer than 60 cases were reported.

Signs and symptoms

Prenatal signs of Seckel syndrome include cranial abnormalities and growth delays (intrauterine growth retardation) resulting in low birth weight. Postnatal growth delays result in dwarfism. Other physical features associated with the disorder include a very small head (often more severely affected than even the height), abnormalities of bones in the arms and legs, malformation of the hips, a permanently bent fifth finger, failure of the testes to descend into the scrotum (for males) and unusual characteristic facial features, including a "beak-like" protrusion of the nose, large eyes, a narrow face, low ears, and an unusually small jaw. Children with the disorder not only have a small head but also a smaller brain, which leads to developmental delay and mental retardation. Seizures have also been reported.

Diagnosis

Several forms of primordial dwarfism exhibit characteristics similar to those of Seckel syndrome, and it can be challenging for physicians to differentiate true Seckel syndrome from other similar dwarfisms. Physicians do have a set of primary diagnostic criteria to follow—the criteria were first defined by Dr. Seckel in 1960 and later revised (1982) to prevent over-diagnosis of cases.

Most of the primary diagnostic features of Seckel syndrome, which include severe intrauterine growth restriction, a small head, characteristic "bird-like" facies, and mental retardation, are well suited for prenatal sonographic diagnosis. The use of ultrasound examinations to evaluate fetal growth and the careful evaluation of the fetal face and cranial anatomy have proven effective at detecting Seckel syndrome.

Treatment and management

There is no cure for Seckel syndrome. Certain medications may be prescribed to address other symptoms associated with the disorder.

Prognosis

Children affected with Seckel syndrome can live for an extended period of time, although they are often faced with profound mental and physical deficits.

Resources

ORGANIZATIONS

Human Growth Foundation. 997 Glen Cove Ave., Glen Head, NY 11545. (800) 451-6434. Fax: (516) 671-4055. <http://www.hgf1@hgfound.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Michelle Lee Brandt

Seckel type dwarfism *see* **Seckel syndrome**

Seemanova syndrome *see* **Nijmegen breakage syndrome**

Seronegative spondyloarthropathies *see* **Ankylosing spondylitis**

Severe atypical spherocytosis due to ankyrine defect *see* **Spherocytosis, hereditary**

Severe combined immunodeficiency

Definition

SCID, or severe combined immunodeficiency, is a group of rare, life-threatening diseases present at birth that impair the immune system. Without a healthy immune system the body cannot fight infections and individuals can easily become seriously ill from common infections.

Description

SCID is one type of Primary Immunodeficiency Diseases (PID) and is considered the most severe. There are approximately 70 forms of PID. Primary immunodeficiency diseases are where a person is missing a component of the immune system—either an organ or cells of the immune sytem. Some deficiencies are deadly, while others are mild.

SCID is also known as the "boy in the bubble" syndrome, because living in a normal enviroment can be fatal. SCID initially was called Swiss agammaglobulinemia because it was first described in Switzerland in 1961. Any exposure to germs can pose a risk for infection, including bacterial, viral, and fungal. In the first few months of life, children with SCID become very ill with infections such as pneumonia (infection of the lungs which prevents oxygen from reaching the blood, making breathing difficult), meningitis (infection of the covering of the brain and spinal cord), sepsis (infection in the bloodstream) and chickenpox, and can die within the first year of life, since their immune system is unable to fight off these infections.

Children with SCID do not respond to medications like other children because their immune system does not function properly. They may also not have a developed thymus gland. Medication usually stimulates a person's immune system to fight infection, but in the case of SCID, the immune system is unable to respond. The immune system is a complex network of cells and organs that protect the body from infection. The thymus and lymphatic system (lymph nodes and lymphatic vessels) house and tranport two very important cells that fight infection: the B and T cells. The bone marrow (center of bones) produces cells that become blood cells as well as cells for the immune system. One type of cell, called lymphocytes or white blood cells, mature in the bone marrow to form "B" cells, while others mature in the thymus to become "T" cells. B and T cells are the two major groups of lymphocytes that recognize and attack infections. Children with SCID have either abnormal or absent B and T cells.

Other infections can be seen in children with SCID including skin infections, yeast infections in the mouth and diaper area, diarrhea, and infection of the liver. Children with SCID fail to gain weight and grow normally. Treatment for SCID is available, however, many children with SCID are not diagnosed in time and die before their first birthday.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid which surrounds a developing baby during pregnancy.

Autosomal recessive inheritance—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Bone marrow transplant (BMT)—A medical procedure used to treat some diseases that arise from defective blood cell formation in the bone marrow. Healthy bone marrow is extracted from a donor to replace the marrow in an ailing individual. Proteins on the surface of bone marrow cells must be identical or very closely matched between a donor and the recipient.

Boy in the bubble—A description for SCID since these children need to be isolated from exposure to germs, until they are treated by bone marrow transplantation or other therapy.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Failure to thrive—Significantly reduced or delayed physical growth.

Gene therapy—Replacing a defective gene with the normal copy.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Lymphatic system—Lymph nodes and lympatic vessels that transport infection fighting cells to the body.

Lymphocytes—Also called white blood cells, lymphocytes mature in the bone marrow to form B cells, which fight infection.

Meningitis—An infection of the covering of the brain.

Pneumonia—An infection of the lungs.

Primary immunodeficiency disease (PID)—A group of approximately 70 conditions that affect the normal functioning of the immune system.

Sepsis—An infection of the bloodstream.

Severe combined immunodeficiency (SCID)—A group of rare, life-threatening diseases present at birth, that cause a child to have little or no immune system. As a result, the child's body is unable to fight infections.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.

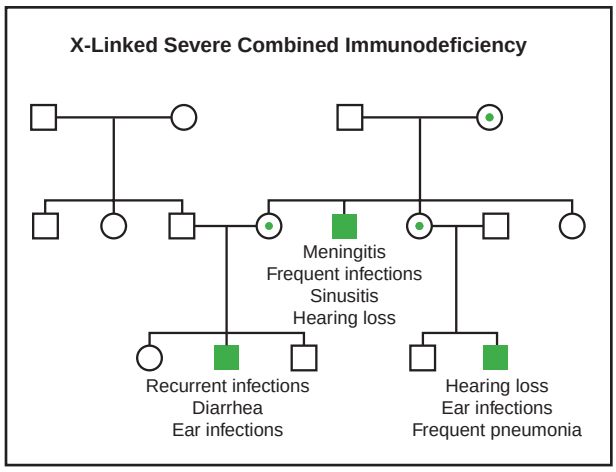
X-linked recessive inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male, passed from a female who has the gene on one of her X chromosomes, who is referred to as an unaffected carrier.

A diagnosis of SCID, besides being painful, frightening, and frustrating, needs to be made quickly since common infections can prove fatal. In addition, permanent damage can result in the ears, lungs, and other organs.

Genetic profile

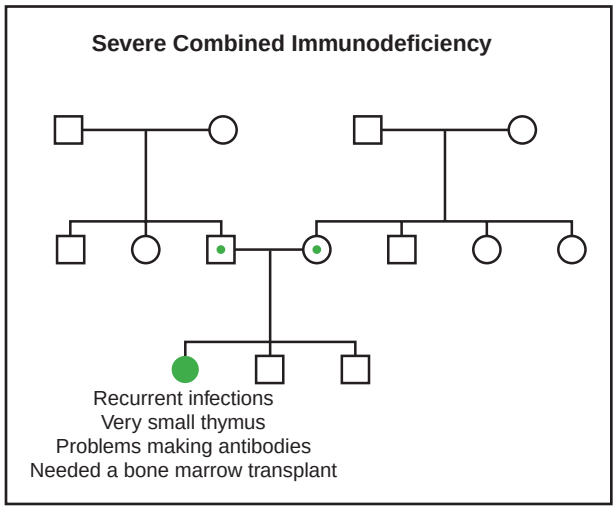
SCID is a group of inherited disorders with about half inherited by a **gene** on the X chromosome called IL2RG, 15% inherited by an autosomal recessive gene called ADA, and the remaining 35% caused by either an unknown autosomal recessive gene or are the result of a new mutation.

Genetic information is carried in tiny packages called **chromosomes**. Each chromosome contains thousands of genes and each gene contains the information for a specific trait. All human cells (except egg and sperm cells)



(Gale Group)

contain 23 pairs of chromosomes for a total of 46 chromosomes. One of each pair of chromosomes is inherited from the mother and the other is inherited from the father. SCID is usually inherited in one of two ways: X-linked recessive or autosomal recessive. Autosomal recessive means that the gene for the disease or trait is located on one of the first 22 pairs of chromosomes, which are also called autosomes. Males and females are equally likely to have an autosomal recessive disease or trait. Recessive means that two copies of the gene are necessary to express the condition. Therefore, a child inherits one copy of the gene from each parent, who are called carriers (because they have only one copy of the gene). Since carriers do not express the gene, parents usually do not know they carry the SCID gene until they have an affected child. Carrier parents have a 1-in-4 chance (or 25%) with each pregnancy, to have a child with SCID.



(Gale Group)

The last pair of human chromosomes, either two X's (female) or one X and one Y (male)—determines gender. X-linked means the gene causing the disease or trait is located on the X chromosome. The term "recessive" usually infers that two copies of a gene—one on each of the chromosome pair—are necessary to cause a disease or express a particular trait. X-linked recessive diseases are most often seen in males, however, because they only have one copy of the X chromosome. Therefore, if a male inherits a particular gene on the X chromosome, he expresses the gene, even though he only has a single copy. Females, on the other hand, have two X chromosomes, and therefore can carry a gene on one of their X chromosomes yet not express any symptoms. (Their second X chromosome copy works normally). A mother usually carries the gene for SCID unknowingly, and has a 50/50 chance with each pregnancy to transmit the gene. If the child is a male, he will have SCID; if the child is female, she will be a carrier for SCID like the mother.

New mutations—alterations in the **DNA** of the gene—can cause disease. In these cases, neither parent has the disease-causing mutation. This may occur because the mutation in the gene happened for the first time only in the egg or sperm for that particular pregnancy. New mutations are thought to happen by chance and are therefore referred to as "sporadic", meaning, by chance.

Demographics

It is estimated that about 400 children a year are born with some type of primary immunodeficiency disease. Approximately one in 100,000 children are born with SCID each year, regardless of the part of the world the child is from, or the ethnic background of the parents. This disease can affect both males and females depending on its mode of **inheritance**.

Signs and symptoms

Babies with SCID fail to thrive, are frail, and do not grow well. They have numerous, serious, life-threatening infections that usually begin in the first few months of life. Because they do not respond to medications like other children, they may be on antibiotics for 1-2 months with no improvement before a physician considers a diagnosis of SCID. The types of infections typically include chronic (developing slowly and persisting for a long period of time) skin infections, yeast infections in the mouth and diaper area, diarrhea, infection of the liver, pneumonia, meningitis, and sepsis. They can also have serious sinus and ear infections, as well as a swollen abdomen. Sometimes deep abscesses occur, which are

pockets of pus that form around infections in the skin or in the body organs.

Diagnosis

About half of children who see a doctor for frequent infections are normal; another 30% may have allergies, 10% have some other type of serious disorder, and 10% have a primary or secondary immunodeficiency. A diagnosis of SCID is usually made based on a complete medical history and physical examination, in addition to multiple blood tests and chest x rays. The gene in X-linked recessive SCID is called the interleukin receptor gamma chain gene or IL2RG. The autosomal recessive forms of SCID are caused by a variety of different genes; one of the more common is called the adenosine deaminase gene or ADA. Since newborns do not routinely have a test to count white blood cells, SCID is not usually suspected and then diagnosed until the child develops their first infection. A pattern of recurrent infections suggests an immunodeficiency.

Once a couple has had a child with SCID, and they have had the genetic cause identified by DNA studies (performed from a small blood sample), prenatal testing for future pregnancies may be considered on a research basis for some types of SCID. (Note that prenatal testing may not be possible if a mutation cannot be identified). Prenatal diagnosis is available via either CVS (chorionic villus sampling) or **amniocentesis**. CVS is a biopsy of the placenta performed in the first trimester or the first 12 weeks of pregnancy under ultrasound guidance. Ultrasound is the use of sound waves to visualize the locations of the developing baby and the placenta. The genetic makeup of the placenta is identical to the fetus (developing baby) and therefore the prescence or absence of one of the SCID genes can be determined from this tissue. Amniocentesis is a procedure performed under ultrasound guidance where a long thin needle is inserted into the mother's abdomen, into the uterus, to withdraw a couple of tablespoons of amniotic fluid (fluid surrounding the developing baby) to study. The SCID gene can be studied using cells from the amniotic fluid. Other genetic tests, such as a chromosome analysis, may also be performed on either a CVS or amniocentesis. A small risk of miscarriage is associated with CVS and amniocentesis.

Treatment and management

The best treatment for SCID is a bone marrow transplant (BMT). A bone marrow transplant involves taking cells that are normally present in bone marrow (the center of bones that produce and store blood cells), and giving them back to the child with SCID or to another person. The goal of BMT is to infuse healthy bone marrow cells into a person after their own unhealthy bone marrow has been eliminated. BMT helps to strengthen a child with SCID's immune system.

Other treatment for SCID includes treating each infection promptly and accurately. Injections are also available to help boost a child's immune system.

In the year 2000, **gene therapy** was first reported to be successful in two French patients with SCID. The idea behind gene therapy is to replace an abnormal gene with a normal copy. In SCID, bone marrow is removed to isolate the patients' stem cells. Stem cells are special cells in the bone marrow that produce lymphocytes. In a laboratory, the normal gene is added to the abnormal stem cells. The genetically altered stem cells now have the normal gene and are transplanted back into the patient. Once the functioning stem cells with the normal gene enter the bone marrow, they reproduce quickly and replace stem cells that have the abnormal gene. So, ultimately, the patient with SCID produces B and T cells normally and can fight off infections without antibiotics or other treatment. The long-term effects of gene therapy are unknown, since the children treated are still very young.

Prognosis

When SCID is diagnosed early, successful bone marrow transplantation usually corrects the problem and the child lives a normal life. This means children can go to school, mix with playmates, and take part in sports. However, the quality of life for individuals with severe cases of SCID can be greatly impaired if they do not receive a bone marrow transplant. Children with SCID may not live long if they do not receive the proper treatment or if their disease goes undiagnosed.

Resources

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Immune Deficiency Foundation. 40 W. Chesapeake Ave., Suite 308, Towson, MD 21204. (800) 296-4433. Fax: (410) 321-9165. <http://www.primaryimmune.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

International Patient Organization for Patients with Primary Immunodeficiencies. <www.ipopi.org>.

Pediatric Primary ImmuneDeficiency. <www.pedpid.com>.
Severed Combined ImmuneDeficiency Homepage. <www.scid.net>.

Catherine L. Tesla, MS, CGC

Short-rib polydactyly

Definition

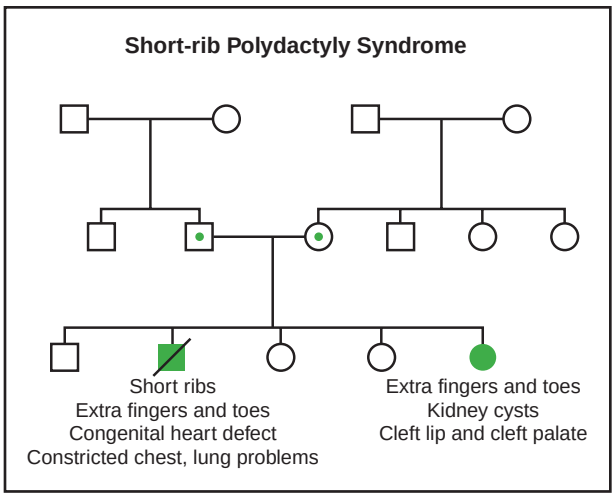
Short-rib polydactyly (SRP) syndromes are a group of skeletal dysplasias consisting of short ribs, short limbs, extra fingers or toes, and various internal organ abnormalities present at birth. There are four types of SRP and all are fatal shortly after birth due to underdevelopment of the lungs.

Description

In 1972, R. M. Saldino and C. D. Noonan first described two siblings with a dwarfism syndrome and symptoms of extremely shortened limbs, short ribs, small chest, abnormal bone formation, extra fingers, and internal organ damage. Since then, three additional SRP subtypes have been identified, all named after those who first described them. The subtypes are: SRP type I (Saldino-Noonan), SRP type II (Majewski), SRP type III (Verma-Namauf), and SRP type IV (Beemer-Langer). While each subtype has distinguishing features, there is a great amount of overlap between them. There is still debate about whether the different types are caused by different genetic changes or if they result from the same genetic change and are variable between patients. Some people believe that the subtypes are different expressions of a single syndrome.

The SRP syndromes also overlap with two other dwarfism syndromes, asphyxiating thoracic **dysplasia** (Jeune syndrome) and Ellis van Creveld syndrome. These syndromes, like the SRP types, have shortened limbs and ribs, small chest, and extra fingers or toes. These syndromes may all be genetically related.

The exact cause of these syndromes is unknown but they all result in abnormal bone development and growth prenatally. This causes shortened bones in the arms, legs, and ribcage. The ribcage is also constricting, leaving very little room for the lung growth. Development can also be abnormal in the internal organs, including the heart, kidneys, liver, and pancreas. The cause of death for these newborns is usually inability to breathe due to severely underdeveloped lungs.



(Gale Group)

Genetic profile

Even though the exact genetic cause of the SRP syndromes is unknown, it is well-documented that they are inherited as autosomal recessive conditions. This is because babies with SRP are born to unaffected parents and many parents have had more than one affected child. Parents of an affected child are assumed to be carriers. Those parents have a 25% chance of having another affected child with each pregnancy.

The **gene** (or genes) involved in the SRP syndromes has not yet been identified but is suspected to be on chromosome 4. Some researchers feel that the SRP gene is near the region of the gene for Ellis van Creveld syndrome on chromosome 4. The gene for another dwarfism syndrome, **thanatophoric dysplasia**, is also located in this area. Research is still being done to find the SRP gene (or genes) and learn more about its role during early development.

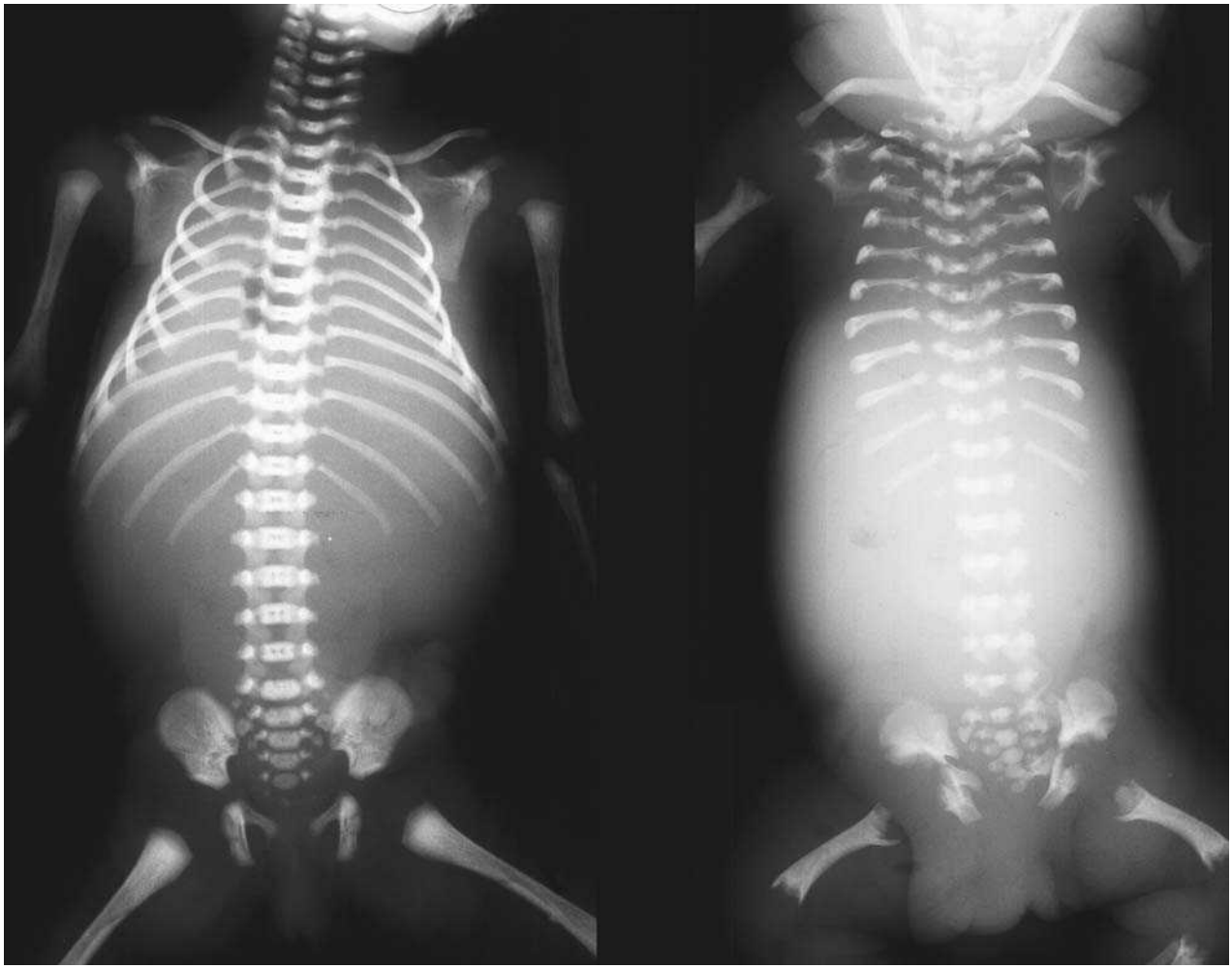
Demographics

Approximately 2-3 births per 10,000 are affected with some type of skeletal dysplasia. The SRP syndromes account for a small percentage of these. Due to the rarity of the SRP syndromes, an exact incidence is unknown.

Signs and symptoms

There is much overlap of symptoms between the SRP subtypes and it is often difficult to distinguish between them. They all have extremely shortened bones of the arms, legs, and ribs. They all also have a small, constricted chest.

Saldino-Noonan (type I) is considered the most severe type. Features reported with this type include spur



These two x rays illustrate the developmental differences between a normal infant (left) and that of an infant with short rib-polydactyly syndrome. *(Greenwood Genetic Center)*

formation on the bones, abnormal vertebrae (bones of the spinal column), and decreased ossification (hardening of the bones). Heart defects are common. Cysts are often seen on the kidneys and pancreas. Extra fingers and/or toes (polydactyly) are a classic feature and are usually on the same side of the hand/foot as the "pinkie" finger/little toe (postaxial). Sex reversal has also been reported. This means that the baby is genetically male but has visible female genitalia.

Majewski (type II) also has cystic kidneys and postaxial polydactyly. This type can also have preaxial polydactyly where the extra fingers/toes are on the same side of the hand/foot as the thumb/big toe. Other distinguishing features include **cleft lip and palate** and liver damage. The tibia (one of the bones of the lower leg) is often oval shaped and shorter than the fibula (the other bone of the lower leg). The ends of the bones may also appear smooth on an x ray.

Verma-Namauf (type III) has much overlap with Saldino-Noonan (type I) and may be a milder variant. Internal organ involvement is less common. The ends of the bones may appear jagged and widened on an x ray. The vertebrae are often small and flat. Polydactyly is also common in this type. Visible genitalia may be ambiguous (not clearly male or female).

Beemer-Langer (type IV), like Majewski, can have cleft lip and palate and liver damage. Cysts on the kidneys and pancreas are common. Polydactyly is usually absent but has been reported. A distinguishing feature of this type is bowed or curved bones.

Diagnosis

Diagnosis of the SRP syndromes can be difficult. A careful examination of internal organs and x ray evaluation is needed to distinguish SRP syndromes from

KEY TERMS

Dwarfism—Any condition that results in extremely shortened limbs.

Skeletal dysplasia—A group of syndromes consisting of abnormal prenatal bone development and growth.

Jeune syndrome and Ellis van Creveld syndrome. When SRP syndrome is suspected, x rays and internal organ involvement can also help to determine the particular type.

The main features of SRP syndromes (short bones, short ribs, small chest) can be seen on prenatal ultrasound. This is the only method of prenatal diagnosis for at-risk families. **Genetic testing** for the SRP syndromes is not available.

Treatment and management

There is no treatment or cure for the SRP syndromes. The abnormal prenatal bone development is irreversible. The chest is usually too small to allow for lung growth after birth. Internal organs with cysts may not be functional.

Infants born with SRP syndromes are given minimum care for warmth and comfort. Due to the poor prognosis, extreme measures to prolong life are rarely taken.

Prognosis

The prognosis for infants born with SRP syndromes is quite poor. These babies usually die within hours or days of birth due to underdeveloped lungs.

Resources

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ORGANIZATIONS

SRPS Family Network. <http://www.srps.net>.

WEBSITES

"Short Rib-Polydactyly Syndrome, Type 1." *Online Mendelian Inheritance in Man.* <http://ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=263530>.

Amie Stanley, MS

Shprintzen-Goldberg craniosynostosis syndrome

Definition

Shprintzen-Goldberg craniosynostosis syndrome (SGS) is a disorder of the connective tissue, featuring **craniosynostosis** and marfanoid body type.

Description

SGS, also known as marfanoid craniosynostosis syndrome, is one of a group of disorders characterized by craniosynostosis and marfanoid body type. It is a condition that involves craniofacial, skeletal, and other abnormalities. SGS is caused by genetic mutations (changes affecting the structure and function of the **gene**) in a gene that contributes to the formation of connective tissue.

Genetic profile

SGS is associated with abnormalities of the elastic fibers of connective tissue. Elastic fibers are complex in structure and are composed of at least 19 different proteins. Mutations in three of the genes that encode the majority of these 19 proteins cause abnormalities in several body systems, including the skeletal system, blood vessels, and eye.

SGS shares characteristics with the **Marfan syndrome**, which is an inherited genetic disorder of the connective tissue which involves the eye, heart, aorta, and skeletal system. Marfan syndrome is caused by mutations in the fibrillin-1 (FBN1) gene, which is located on chromosome 15. Since SGS is similar in many ways to Marfan syndrome, studies of the FBN1 gene were conducted on SGS patients to see if they also had mutations in this gene. There were indeed abnormalities found in the FBN1 genes of persons with SGS. Researchers think that these mutations predispose a person to develop SGS, but that other factors are required in addition to the mutation in the gene to develop the disease. The other factors may be genetic mutations, environmental influences, or a combination of these, but they are not well-understood at this time.

The mutations appear to be sporadic in nature (not inherited), and are autosomal dominant (only one mutation is necessary to be predisposed to the disease). Sporadic genetic mutations in the sperm occur (in any gene, not just FBN1) at a higher rate in older men (over 45 years) and there is in fact one case report of a child with SGS in which the father was 49 years old. The father of another child with SGS reportedly had chemotherapy and radiation treatment prior to conception of the child.

The recurrence risk for siblings is probably low, although such data is not available.

Demographics

There are 15 reported cases as of 2000, with the first case being described in 1981. The ratio of females to males is 10:5, making females affected twice as often as males. Ethnicities would be expected to be affected equally with sporadic mutations, although data regarding SGS specifically is limited.

Signs and symptoms

Findings in SGS include skeletal abnormalities, **hydrocephalus**, and mental retardation. Most babies have been born well-nourished and had a relatively long birth length. The most frequently described craniofacial features of SGS include abnormal head shape (dolichocephaly), a high, prominent forehead, bulging eyes (ocular proptosis), wide spaced eyes (hypertelorism), downslanting eyes, strabismus (wandering eye), small jaw (maxillary hypoplasia), high narrow palate (roof of the mouth), and low-set ears.

The main skeletal findings in persons with SGS include long, thin fingers (arachnodactyly—or spider-like fingers), flat feet (pes planus), "bird" chest deformity (pectus deformity), **scoliosis** (curvature of the spine), and joint hypermobility (loose joints).

Other features can include **clubfoot**, enlarged aortic root, mitral valve prolapse (floppy heart valve which allows flow of blood back into the chamber of the heart that it came from), low muscle tone (hypotonia), developmental delay, mental retardation, very little body fat, and small penis in males. **Myopia** (near-sightedness) and abdominal wall defects (developmental problem that occurs during formation of the fetus where parts of the intestine or other organs can protrude outside of the body; usually surgically correctable) can also occur.

Radiologic findings include hydrocephalus (water on the brain), certain brain malformations (Chiari-I malformation or dilatation of the lateral ventricles), abnormalities in the first and second cervical vertebrae (vertebrae in the neck), square shaped vertebrae, thin ribs, thinning of the bones, and craniofacial abnormalities.

Diagnosis

There are more than 75 syndromes associated with craniosynostosis. There are also a number of different syndromes associated with both craniosynostosis and marfanoid body type. X-ray evaluation can be helpful in determining whether a person has SGS, as they tend to have abnormal first and second cervical vertebrae, hydrocephalus (water on the brain), and certain brain malformations.

KEY TERMS

Aortic root—The location where the aorta (main heart blood vessel) inserts in the heart. Enlargement of the aortic root can cause it to rupture.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Marfanoid—Term for body type which is similar to people with Marfan syndrome. Characterized by tall, lean body with long arms and long fingers.

SGS must be differentiated from other syndromes with craniosynostosis and marfaniod body type. Two such syndromes include Idaho syndrome II and Antley-Bixler syndrome. Idaho syndrome II has less severe craniofacial problems than SGS and has abnormal leg bones and absent patellae (knee caps). Antley-Bixler syndrome is an inherited syndrome with craniofacial abnormalities, abnormal arm and leg bones, and fractures in the femurs (thigh bones). These characteristics are different from SGS. A clinical geneticist is a physician who has special training in recognizing and diagnosing rare genetic conditions and is a good resource for differentiating among these complicated and similar conditions.

Treatment and management

Cardiology evaluation is important since several children have been reported to have severe cardiac disease with SGS. Aortic root must be evaluated and measured routinely to minimize the risk for rupture. Enlarged aortic roots may need to be surgically repaired.

Patients should have an opthalmalogic evaluation, since mutations in the FBR1 gene are associated with abnormalities in the eyes.

Surgical correction of craniofacial problems or pectus are sometimes necessary or desirable. Shunting (surgical placement of a shunt to drain the accumulated fluid in the brain to the abdominal cavity to relieve pressure) may be required for patients with hydrocephalus. Orthopedic devices may be required for scoliosis or other bone abnormalities.

Special education for mentally retarded individuals or individuals with developmental delay is recommended.

Genetic counseling is recommended for persons with relatives diagnosed with SGS.

Prognosis

SGS does not alter lifespan, although complications from associated abnormalities such as mental retardation or respiratory problems can cause problems.

Resources

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Lee, Y.C., et al. "Marfanoid Habitus, Dysmorphic Features, and Web Neck." *Southerna Medical Journal* 93 (2000): 1197-1200

ORGANIZATIONS

Coalition for Heritable Disorders of Connective Tissue (CHDCT). 382 Main Street, Port Washington, NY 11050. (516) 883-8712. <http://www.chdct.org>.

Hydrocephalus Association. 870 Market St. Suite 705, San Francisco, CA 94102. (415) 732-7040 or (888) 598-3789. Fax: (415) 732-7044. hydroassoc@aol.com. <http://www.hydroassoc.org>.

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Amy Vance, MS, CGC

Sialidoses types I and II *see* **Neuraminidase deficiency**

Sickle cell disease

Definition

Sickle cell disease describes a group of inherited blood disorders characterized by chronic anemia, painful events, and various complications due to associated tissue and organ damage.

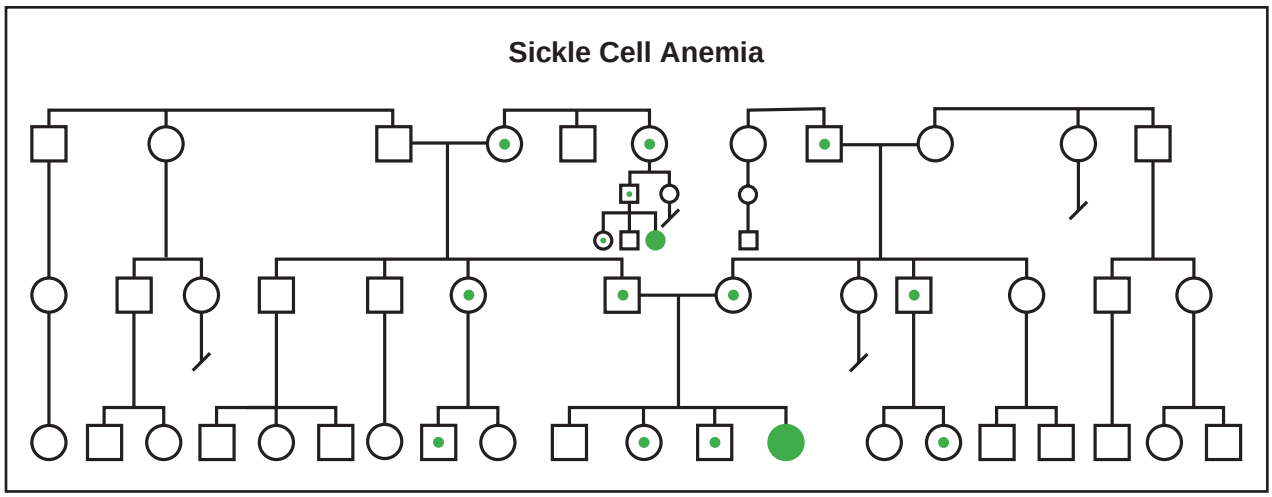
Description

The most common and well-known type of sickle cell disease is sickle cell anemia, also called SS disease. All types of sickle cell disease are caused by a genetic change in hemoglobin, the oxygen-carrying protein inside the red blood cells. The red blood cells of affected individuals contain a predominance of a structural variant of the usual adult hemoglobin. This variant hemoglobin, called sickle hemoglobin, has a tendency to develop into rod-like structures that alter the shape of the usually flexible red blood cells. The cells take on a shape that resembles the curved blade of the sickle, an agricultural tool. Sickle cells have a shorter life span than normally-shaped red blood cells. This results in chronic anemia characterized by low levels of hemoglobin and decreased numbers of red blood cells. Sickle cells are also less flexible and more sticky than normal red blood cells, and can become trapped in small blood vessels preventing blood flow. This compromises the delivery of oxygen, which can result in pain and damage to associated tissues and organs. Sickle cell disease presents with marked variability, even within families.

Demographics

Carriers of the sickle cell **gene** are said to have sickle cell trait. Unlike sickle cell disease, sickle cell trait does not cause health problems. In fact, sickle cell trait is protective against malaria, a disease caused by blood-borne parasites transmitted through mosquito bites. According to a widely accepted theory, the genetic mutation associated with the sickle cell trait occurred thousands of years ago. Coincidentally, this mutation increased the likelihood that carriers would survive malaria infection. Survivors then passed the mutation on to their offspring, and the trait became established throughout areas where malaria was common. As populations migrated, so did the sickle cell trait. Today, approximately one in 12 African Americans has sickle cell trait.

Worldwide, it has been estimated that one in every 250,000 babies is born annually with sickle cell disease. Sickle cell disease primarily affects people of African, Mediterranean, Middle Eastern, and Asian Indian ancestry. In the United States, sickle cell disease is most often seen in African Americans, in whom the disease occurs in one out of every 400 births. The disease has been described in individuals from several different ethnic backgrounds and is also seen with increased frequency in Latino Americans—particularly those of Caribbean, Central American, and South American ancestry. Approximately one in every 1,000-1,400 Latino births are affected.



(Gale Group)

Genetic profile

Humans normally make several types of the oxygen-carrying protein hemoglobin. An individual's stage in development determines whether he or she makes primarily embryonic, fetal, or adult hemoglobins. All types of hemoglobin are made of three components: heme, alpha (or alpha-like) globin, and beta (or beta-like) globin. Sickle hemoglobin is the result of a genetic change in the beta globin component of normal adult hemoglobin. The beta globin gene is located on chromosome 11. The sickle cell form of the beta globin gene results from the substitution of a single **DNA** nucleotide, or genetic building-block. The change from adenine to thymine at codon (position) 6 of the beta globin gene leads to insertion of the amino acid valine—instead of glutamic acid—at this same position in the beta globin protein. As a result of this change, sickle hemoglobin has unique properties in comparison to the usual type of adult hemoglobin.

Most individuals have two normal copies of the beta globin gene, which make normal beta globin that is incorporated into adult hemoglobin. Individuals who have sickle cell trait (called sickle cell carriers) have one normal beta globin gene and one sickle cell gene. These individuals make both the usual adult hemoglobin and sickle hemoglobin in roughly equal proportions, so they do not experience any health problems as a result of having the trait. Although traces of blood in the urine and difficulty in concentrating the urine can occur, neither represents a significant health problem as a result of sickle cell trait. Of the millions of people with sickle cell trait worldwide, a small handful of individuals have experienced acute symptoms. In these very rare cases, individuals were subject to very severe physical strain.

When both members of a couple are carriers of sickle cell trait, there is a 25% chance in each pregnancy for the baby to inherit two sickle cell genes and have sickle cell anemia, or SS disease. Correspondingly, there is a 50% chance the baby will have sickle cell trait and a 25% chance that the baby will have the usual type of hemoglobin.

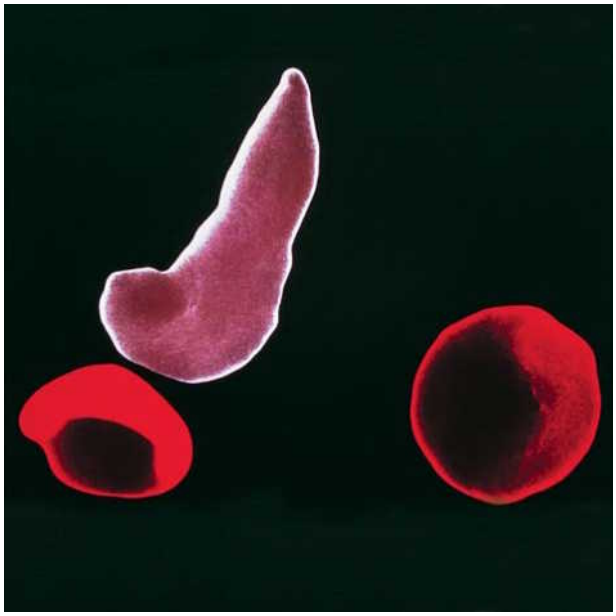
Other types of sickle cell disease include SC disease, SD disease, and S/beta thalassemia. These conditions are caused by the co-inheritance of the sickle cell gene and another altered beta globin gene. For example, one parent may have sickle cell trait and the other parent may have hemoglobin C trait (another hemoglobin trait that does not cause health problems). For this couple, there would be a 25% chance of SC disease in each pregnancy.

Signs and symptoms

Normal adult hemoglobin transports oxygen from the lungs to tissues throughout the body. Sickle hemoglobin can also transport oxygen. However, once the oxygen is released, sickle hemoglobin tends to polymerize (line-up) into rigid rods that alter the shape of the red blood cell. Sickling of the red blood cell can be triggered by low oxygen, such as occurs in organs with slow blood flow. It can also be triggered by cold temperatures and dehydration.

Sickle cells have a decreased life span in comparison to normal red blood cells. Normal red blood cells survive for approximately 120 days in the bloodstream; sickle cells last only 10-12 days. As a result, the bloodstream is chronically short of red blood cells and hemoglobin, and the affected individual develops anemia.

Sickle cells can create other complications. Due to their shape, they do not fit well through small blood



Scanning electron micrograph (SEM) of red blood cells taken from a person with sickle cell anemia. The red blood cells at the bottom are normal; the diseased, sickle-shaped cell appears at the top. *(Photo Researchers, Inc.)*

vessels. As an aggravating factor, the outside surfaces of sickle cells may have altered chemical properties that increase the cells' 'stickiness'. These sticky sickle cells are more likely to adhere to the inside surfaces of small blood vessels, as well as to other blood cells. As a result of the sickle cells' shape and stickiness, blockages form in small blood vessels. Such blockages prevent oxygenated blood from reaching areas where it is needed, causing pain as well as organ and tissue damage.

The severity of symptoms cannot be predicted based solely on the genetic **inheritance**. Some individuals with sickle cell disease develop health- or life-threatening problems in infancy, but others may have only mild symptoms throughout their lives. Individuals may experience varying degrees of health at different stages in the lifecycle. For the most part, this clinical variability is unpredictable, and the reasons for the observed variability can not usually be determined. However, certain types of sickle cell disease (i.e. SC disease) tend to result in fewer and less severe symptoms on average than other types of sickle cell disease (i.e. SS disease). Some additional modifying factors are known. For example, elevated levels of fetal hemoglobin in a child or adult can decrease the quantity and severity of some symptoms and complications. Fetal hemoglobin is a normally occurring hemoglobin that usually decreases from over 90% of the total hemoglobin to under one percent during the first year of life. This change is genetically determined, although some individuals may experience elevated levels of fetal hemoglobin due to variation in the genes that control fetal hemoglobin production. Such individuals often experience a reduction in their symptoms and complications due to the ability of fetal hemoglobin to prevent the polymerization of sickle hemoglobin, which leads to sickling of the red blood cell.

There are several symptoms that warrant immediate medical attention, including the following:

- Signs of infection (fever greater than 101°F or 38.3°C, coughs frequently or breathing trouble, unusual crankiness, feeding difficulties)
- Signs of severe anemia (pale skin or lips, yellowing of the skin or eyes, very tired, very weak)
- Signs indicating possible dehydration (vomiting, diarrhea, fewer wet diapers)
- Other signs (pain or swelling in the abdomen, swollen hands or feet, screams when touched).

These can be signs of various complications that occur in sickle cell disease.

Infections and effects on the spleen

Children with sickle cell disease who are under age three are particularly prone to life-threatening bacterial infections. *Streptococcus pneumoniae* is the most common offending bacteria, and invasive infection from this organism leads to death in 15% of patients. The spleen, an organ that helps to fight bacterial infections, is particularly vulnerable to the effects of sickling. Sickle cells can impede blood flow through the spleen, causing organ damage, which usually results in loss of spleen function by late childhood. The spleen can also become enlarged due to blockages and/or increased activity of the spleen. Rapid enlargement of the spleen may be a sign of another complication called *splenic sequestration*, which occurs mostly in young children and can be life-threatening. Widespread sickling in the spleen prevents adequate blood flow from the organ, removing increasing volumes of blood from the circulation and leading to accompanying signs of severe anemia.

Painful events

Painful events, also known as *vaso-occlusive events*, are a hallmark symptom of sickle cell disease. The frequency and duration of the pain can vary tremendously from person to person and over an individual's lifecycle. Painful events are the most common cause of hospitalizations in sickle cell disease. However, only a small portion of individuals with sickle cell disease experience frequent and severe painful events. Most painful events can be managed at home. Pain results when small blood

vessel blockages prevent oxygen from reaching tissues. Pain can affect any area of the body, although the extremities, chest, abdomen, and bones are frequently affected sites. There is some evidence that cold temperatures or infection can trigger a painful event, but most events occur for unknown reasons. The hand-foot syndrome, or *dactylitis*, is a particular type of painful event. Most common in toddlers, dactylitis results in pain and swelling in the hands and feet, sometimes accompanied by a fever.

Anemia

Sickle cells have a high turnover rate leading to a deficit of red blood cells in the bloodstream. Common symptoms of anemia include fatigue, paleness, and a shortness of breath. A particularly severe form of anemia—aplastic anemia—occurs following infection with parvovirus. Parvovirus causes extensive destruction of the bone marrow, bringing production of new red blood cells to a halt. Bone marrow production resumes after seven to 10 days; however, given the short lives of sickle cells, even a brief shut-down in red blood cell production can cause a rapid decline in hemoglobin concentrations.

Delayed growth

The energy demands of the bone marrow for red blood cell production compete with the demands of a growing body. Children with sickle cell anemia may have delayed growth and reach puberty at a later age than normal. By early adulthood, they catch up on growth and attain normal height; however, weight typically remains below average.

Stroke

Children with sickle cell disease have a significantly elevated risk of having a stroke, which can be one of the most concerning complications of sickle cell disease. Approximately 11% of individuals with sickle cell disease will have a recognizable stroke by the age of 20. Magnetic resonance imaging studies have found that 17% of children with sickle cell anemia have evidence of a previous stroke or clinically ‘silent’ stroke-like events called *transient ischemic events*. Stroke in sickle cell disease is usually caused by a blockage of a blood vessel, but about one fourth of the time may be caused by a hemorrhage (or rupture) of a blood vessel.

Strokes result in compromised delivery of oxygen to an area of the brain. The consequences of stroke can range from life-threatening, to severe physical or cognitive impairments, to apparent or subtle learning disabilities, to undetectable effects. Common stroke symptoms include weakness or numbness that affects one side of the body, sudden behavioral changes, loss of vision, confusion, loss of speech or the ability to understand spoken words, dizziness, headache, seizures, vomiting, or even coma.

Approximately two-thirds of the children who have a stroke will have at least one more. Transfusions have been shown to decrease the incidence of a second stroke. A recent study showed that children at highest risk to experience a first stroke were 10 times more likely to stroke if untreated when compared to high-risk children treated with chronic blood transfusion therapy. High-risk children were identified using transcranial doppler ultrasound technology to detect individuals with increased blood flow speeds due to constricted intracranial blood vessels.

Acute chest syndrome

Acute chest syndrome (ACS) is a leading cause of death for individuals with sickle cell disease, and recurrent attacks can lead to permanent lung damage. Therefore, rapid diagnosis and treatment is of great importance. ACS can occur at any age and is similar but distinct from pneumonia. Affected persons may experience fever, cough, chest pain, and shortness of breath. ACS seems to have multiple causes including infection, sickling in the small blood vessels of the lungs, fat embolisms in the lungs, or a combination of factors.

Priapism

Males with sickle cell anemia may experience priapism, a condition characterized by a persistent and painful erection of the penis. Due to blood vessel blockage by sickle cells, blood is trapped in the tissue of the penis. Priapism may be short in duration or it may be prolonged. Priapism can be triggered by low oxygen (hypoxemia), alcohol consumption, or sexual intercourse. Since priapism can be extremely painful and result in damage to this tissue causing impotence, rapid treatment is essential.

Kidney disease

The environment in the kidney is particularly prone to damage from sickle cells. Signs of kidney damage can include blood in the urine, incontinence, and enlarged kidneys. Adults with sickle cell disease often experience insufficient functioning of the kidneys, which can progress to kidney failure in a small percentage of adults with sickle cell disease.

Jaundice and gallstones

Jaundice is indicated by a yellow tone in the skin and eyes, and alone it is not a health concern. Jaundice may occur if bilirubin levels increase, which can occur with high levels of red blood cell destruction. Bilirubin is the

final product of hemoglobin degradation, and is typically removed from the bloodstream by the liver. Therefore, jaundice can also be a sign of a poorly functioning liver, which may also be evidenced by an enlarged liver. Increased bilirubin also leads to increased chance for gallstones in children with sickle cell disease. Treatment, which may include removal of the gall bladder, may be selected if the gallstones start causing symptoms.

Retinopathy

The blood vessels that supply oxygen to the retina—the tissue at the back of the eye—may be blocked by sickle cells, leading to a condition called retinopathy. This is one of the only complications that is actually more common in SC disease as compared to SS disease. Retinopathy can be identified through regular ophthalmology evaluations and effectively treated in order to avoid damage to vision.

Joint problems

Avascular necrosis of the hip and shoulder joints, in which bone damage occurs due to compromised blood flow due to sickling, can occur later in childhood. This complication can affect an individual's physical abilities and result in substantial pain.

Diagnosis

Inheritance of sickle cell disease or trait cannot be prevented, but it may be predicted. Screening is recommended for individuals in high-risk populations. In the United States, African Americans and Latino Americans have the highest risk of having the disease or trait. Sickle cell is also common among individuals of Mediterranean, Middle Eastern, and Eastern Indian descent.

A complete blood count (CBC) will describe several aspects of an individual's blood cells. A person with sickle cell disease will have a lower than normal hemoglobin level, together with other characteristic red blood cell abnormalities. A *hemoglobin electrophoresis* is a test that can help identify the types and quantities of hemoglobin made by an individual. This test uses an electric field applied across a slab of gel-like material. Hemoglobins migrate through this gel at various rates and to specific locations, depending on their size, shape, and electrical charge. Although sickle hemoglobin (Hb S) and regular adult hemoglobin (called Hb A) differ by only one amino acid, they can be clearly separated using hemoglobin electrophoresis. *Isoelectric focusing* and *high-performance liquid chromatography (HPLC)* use similar principles to separate hemoglobins and can be used instead of or in various combinations with hemoglobin electrophoresis to determine the types of hemoglobin present.

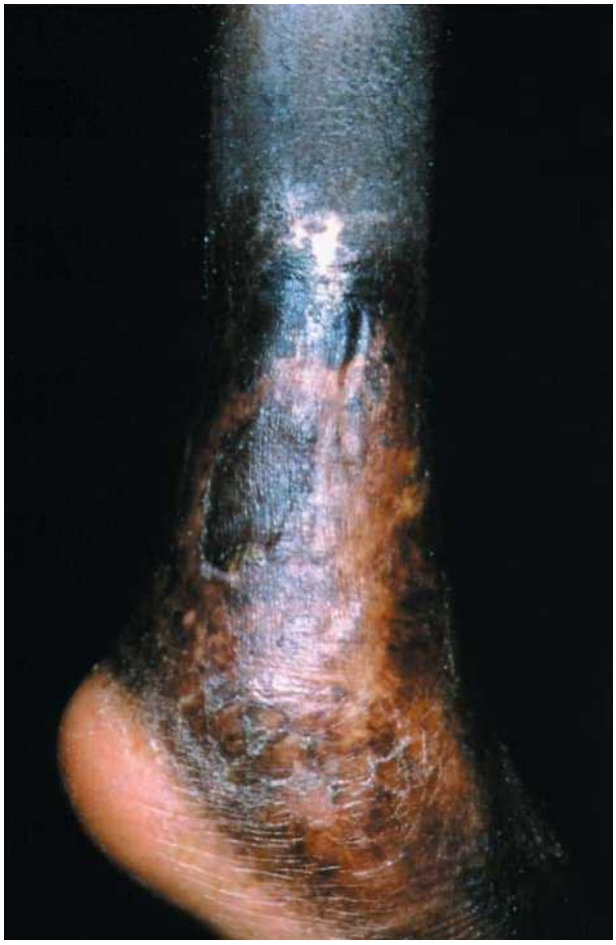
Another test, called the 'sickledex' can help confirm the presence of sickle hemoglobin, although this test cannot provide accurate or reliable diagnosis when used alone. When Hb S is present, but there is an absence or only a trace of Hb A, sickle cell anemia is a likely diagnosis. Additional beta globin DNA testing, which looks directly at the beta globin gene, can be performed to help confirm the diagnosis and establish the exact genetic type of sickle cell disease. CBC and hemoglobin electrophoresis are also typically used to diagnosis sickle cell trait and various other types of beta globin traits.

Diagnosis of sickle cell disease can occur under various circumstances. If an individual has symptoms that are suggestive of this diagnosis, the above-described screening tests can be performed followed by DNA testing, if indicated. Screening at birth using HPLC or a related technique offers the opportunity for early intervention. More than 40 states include sickle cell screening as part of the usual battery of blood tests done for newborns. This allows for early identification and treatment. Hemoglobin trait screening is recommended for any individual of a high-risk ethnic background who may be considering having children. When both members of a couple are found to have sickle cell trait, or other related hemoglobin traits, they can receive **genetic counseling** regarding the risk of sickle cell disease in their future children and various testing options.

Sickle cell disease can be identified before birth through the use of prenatal diagnosis. Chorionic villus sampling (CVS) can be offered as early as 10 weeks of pregnancy and involves removing a sample of the placenta made by the baby and testing the cells. CVS carries a risk of causing a miscarriage that is between one-half to one percent.

Amniocentesis is generally offered between 16 and 18 weeks of pregnancy, but can sometimes be offered earlier. Two to three tablespoons of the fluid surrounding the baby is removed. This fluid contains fetal cells that can be tested. This test carries a risk of causing a miscarriage, which is less than one percent. Pregnant woman and couples may choose prenatal testing in order to prepare for the birth of a baby that may have sickle cell disease.

Preimplantation genetic diagnosis (PGD) is a relatively new technique that involves in-vitro fertilization followed by **genetic testing** of one cell from each developing embryo. Only the embryos unaffected by sickle cell disease are transferred back into the uterus. PGD is currently available on a research basis only, and is relatively expensive.



The lower leg of this woman has ulcerated, necrotic tissue, resulting from sickle cell anemia. *(Custom Medical Stock Photo, Inc.)*

Treatment and management

There are several practices intended to prevent some of the symptoms and complications of sickle cell disease. These include preventative antibiotics, good hydration, immunizations, and access to comprehensive care. Maintaining good health through adequate nutrition, avoiding stresses and infection, and getting proper rest is also important. Following these guidelines is intended to improve the health of individuals with sickle cell disease.

Penicillin

Infants are typically started on a course of penicillin that extends from infancy to age six. Use of this antibiotic is meant to ward off potentially fatal infections. Infections at any age are treated aggressively with antibiotics. Vaccines for common infections, such as *pneumococcal pneumonia*, are also recommended.

Pain management

Pain is one of the primary symptoms of sickle cell anemia, and controlling it is an important concern. The methods necessary for pain control are based on individual factors. Some people can gain adequate pain control through over-the-counter oral painkillers (analgesics). Other individuals, or painful events, may require stronger methods which can include administration of narcotics. Alternative therapies may be useful in avoiding or controlling pain, including relaxation, hydration, avoiding extremes of temperature, and the application of local warmth.

Blood transfusions

Blood transfusions are not usually given on a regular basis but are used to treat individuals with frequent and severe painful events, severe anemia, and other emergencies. In some cases blood transfusions are given as a preventative measure, for example to treat spleen enlargement or prevent a second stroke (or a first stroke in an individual shown to be at high risk).

Regular blood transfusions have the potential to decrease formation of hemoglobin S, and reduce associated symptoms. However, there are limitations and risks associated with regular blood transfusions, including the risk of blood-borne infection and sensitization to proteins in the transfused blood that can make future transfusions very difficult. Most importantly, chronic blood transfusions can lead to iron overload. The body tends to store excess iron, such as that received through transfusions, in various organs. Over time, this iron storage can cause damage to various tissues and organs, such as the heart and endocrine organs.

Some of this damage can be prevented by the administration of a medication called *desferoxamine* that helps the body to eliminate excess iron through the urine. Alternately, some individuals receive a new, non-standard treatment called *erythrocytapheresis*. This involves the automated removal of sickle cells and is used in conjunction with a reduced number of regular transfusions. This treatment helps to reduce iron overload.

Hydroxyurea

Emphasis is being placed on developing drugs that treat sickle cell anemia directly. The most promising of these drugs since the late 1990s has been hydroxyurea, a drug that was originally designed for anticancer treatment. Hydroxyurea has been shown to reduce the frequency of painful crises and acute chest syndrome in adults, and to lessen the need for blood transfusions. Hydroxyurea, and other related medications, seem to work by inducing a higher production of fetal hemoglobin. The major side

effects of the drug include decreased production of platelets, red blood cells, and certain white blood cells. The effects of long-term hydroxyurea treatment are unknown.

Bone marrow transplantation

Bone marrow transplantation has been shown to cure sickle cell anemia in some cases. This treatment is reserved primarily for severely affected children with a healthy donor whose marrow proteins match those of the recipient, namely a brother or sister who has inherited the same tissue type. Indications for a bone marrow transplant are stroke, recurrent acute chest syndrome, and chronic unrelieved pain.

Bone marrow transplantations tend to be the most successful in children; adults have a higher rate of transplant rejection and other complications. There is approximately a 10% fatality rate associated with bone marrow transplants done for sickle cell disease. Survivors face potential long-term complications, such as chronic graft-versus-host disease (an immune-mediated attack by the donor marrow against the recipient's tissues), infertility, and development of some forms of **cancer**. A relatively recent advance in transplantation involves the use of donor stem cells obtained from *cord blood*, the blood from the placenta that is otherwise discarded following the birth of a new baby. Cord blood cells, as opposed to fully mature bone marrow cells, appear to be less likely to result in graft-versus-host disease in the recipient. This increases the safety and efficacy of the transplant procedure.

Surgery

Certain surgical interventions are utilized in the treatment of specific sickle cell-related complications. Removal of a dysfunctioning gallbladder or spleen can often lead to improvements in health. Investigations are currently underway to establish the efficacy of hip coring surgery, in which a portion of affected bone is removed to treat avascular necrosis of the hip. The hope is that this may provide an effective treatment to alleviate some pain and restore function in the affected hip.

Psychosocial support

As in any lifelong, chronic disease, comprehensive care is important. Assistance with the emotional, social, family-planning, economic, vocational, and other consequences of sickle cell disease can enable affected individuals to better access and benefit from their medical care.

Prognosis

Sickle cell disease is characteristically variable between and within affected individuals. Predicting the course of the disorder based solely on genes is not possible. Several factors aside from genetic inheritance determine the prognosis for affected individuals, including the frequency, severity, and nature of specific complications in any given individual. The availability and access of comprehensive medical care also plays an important role in preventing and treating serious, acute complications, which cause the majority of sickle cell-related deaths. For those individuals who do not experience such acute events, life-expectancy is probably substantially greater than the average for all people with sickle cell disease. The impact of recent medical advances supports the hypothesis that current life-expectancies may be significantly greater than those estimated in the early 1990s. At that time, individuals with SS disease lived to the early- to mid-40s, and those with SC disease lived into the upper 50s on average. With early detection and comprehensive medical care, most people with sickle cell disease are in fairly good health most of the time. Most individuals can be expected to live well into adulthood, enjoying an improved quality of life including the ability to choose a variety of education, career, and family-planning options for themselves.

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ORGANIZATIONS

Sickle Cell Disease Association of America, Inc. 200 Corporate Point Suite 495, Culver City, CA 90230-8727. (800) 421-8453. Scdaa@sicklecelldisease.org. <http://sicklecelldisease.org/>.

Jennifer Bojanowski, MS, CGC

Siewert syndrome *see* **Kartagener syndrome**

Silver-Russell syndrome *see* **Russell-Silver syndrome**

Simpson dysmorphia syndrome (SDYS) *see* **Simpson-Golabi-Behmel syndrome**

Simpson-Golabi-Behmel syndrome

Definition

Simpson-Golabi-Behmel syndrome (SGBS) is a rare X-linked recessive inherited condition. It causes general overgrowth in height and weight. Individuals with SGBS also have characteristic facial features in childhood which tend to become less obvious in adulthood.

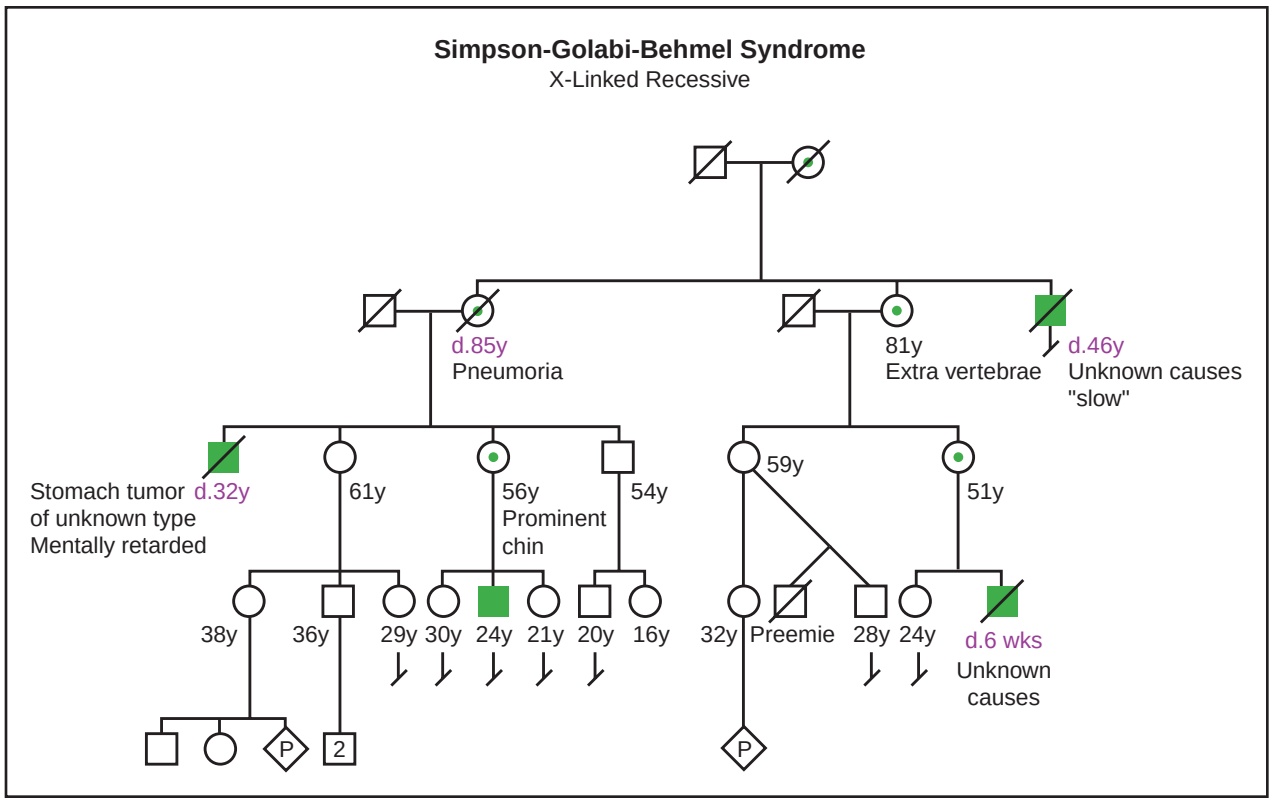
Description

SGBS is also known as Simpson dysmorphia syndrome (SDYS), bulldog syndrome, Golabi-Rosen syndrome, and dysplasia gigantism syndrome X-linked (DGSX). SGBS is a rare X-linked recessive inherited condition. Individuals with this condition have increased height and weight for their age; a broad, stocky appearance; a large protruding jaw; a short, broad nose; incomplete closure of the roof of the mouth (cleft palate); and broad, short hands and fingers. Individuals with SGBS are usually taller than average. The characteristic features usually become less apparent in adulthood. There are at least two genes for SGBS. Both genes are located on the X chromosome.

Genetic profile

SGBS is caused by an alteration (mutation) in one of two genes on the X chromosome. **Chromosomes** are units of hereditary material passed from a parent to a child through the egg and sperm. The information on the chromosomes is organized into units called genes. Genes contain information necessary for normal human growth and development. Each cell in the body usually contains 46 chromosomes, arranged as 23 pairs. Twenty-two pairs of chromosomes are the same in males and females. The twenty-third pair is the sex chromosomes: females have two X chromosomes and males have an X and a Y chromosome. There are two genes on the X chromosome that can cause SGBS. The first **gene** is responsible for making a protein called glypican-3 (GPC3). The exact role of GPC3 is not known but it is thought to play a role in growth and development. When the gene for GPC3 is altered, the signs and symptoms of SGBS result. A second candidate gene, which causes a more severe form of SGBS, is also located on the X chromosome. The function of this second gene is not known. Generally, individuals who have SGBS due to a gene alteration in the GPC3 gene are said to have SGBS type 1 (SGBS1) and individuals who have SGBS due to an alteration in the second gene on the X chromosome are said to have SGBS type 2 (SGBS2).

SGBS is inherited as an X-linked recessive condition. With X-linked recessive conditions, males are usually more severely affected than females. Females have two copies of the SGBS gene (because they have two X chromosomes) while males have one copy of SGBS gene (because they have one X chromosome). Females who have an alteration in one copy of the SGBS gene are said to be *carriers* of SGBS. Generally, carriers show minimal or no effects of the altered gene because they have a second normal copy of the gene that is able to compensate for the altered copy. Since males have only one working copy of the SGBS gene to start, if that gene is altered, they will develop SGBS. When carrier females have children, they are at risk to have a child with SGBS. In each pregnancy, carrier females have a 25% chance of having a child (always a son) with SGBS and a 25% chance of having a child (always a daughter) whom is a carrier of SGBS. Males who are affected with SGBS cannot pass



(Gale Group)

this condition to their sons (because their sons inherit the Y chromosome); however, all daughters of a male affected with SGBS will be carriers for the condition.

Demographics

SGBS is a rare inherited condition that primarily affects males from all ethnic groups. Female carriers for SGBS may show subtle features of the condition. It is not known precisely how many individuals are affected with SGBS.

Signs and symptoms

The spectrum of clinical features in SGBS is broad, ranging from very mild forms in carrier females to forms that are lethal in the newborn male. SGBS affects the face, hands, chest, abdomen, genitals, internal organs and overall growth.

Individuals with SGBS are larger than average at birth in height, weight, and head size. This overgrowth continues into adulthood with affected males being taller than average. Final height in males ranges from 74 in to 83 in (188 cm to 210 cm). There are typical facial characteristics in affected males including widely spaced eyes, short nose, large mouth, large tongue, a groove in the lower lip, and teeth that do not align properly. Incomplete closure of the lip (cleft lip) and/or the roof of the mouth (cleft palate) can also occur. The large tongue and improperly aligned teeth can be a cause of speech difficulties.

The hands and feet of males with SGBS tend to be short and broad. Other hand abnormalities such as small nails, webbing of the skin between the fingers, and extra fingers/toes, is also common. Males with SGBS have extra nipples and some may have undescended testicles.

The internal organs are larger than average, particularly the liver, spleen, and kidneys. The kidneys may also have many cysts on them. A few individuals have been known to have lung and diaphragm abnormalities. Heart abnormalities can also occur in SGBS1 and have been a cause of death in several individuals under two years of age. These include conduction defects causing arrythmias. The stomach and intestines can also be affected, which may cause digestive problems. The bones may also be affected. Some individuals have an abnormal curving and twisting of the spine (**scoliosis**), extra ribs, and/or problems with the structure of the bones of the spine. The bony changes can be seen on x ray but may not cause any symptoms.

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Despite their large size, newborns with SGBS tend to be floppy babies with decreased muscle tone. Due to this low muscle tone, there are several features that can result such as mouth breathing, a deformity of the chest wall (pectus excavatum), shoulders that droop, hernias, and undescended testicles.

There is an increased risk to develop tumors of the kidney (Wilms tumor) in SGBS in early childhood. This risk appears to be greatest in individuals under two years of age.

Most individuals with SGBS are of average intelligence, although some degree of mental impairment has been observed in males who are more severely affected. Individuals with SGBS may have psychological difficulties dealing with their distinctive facial appearance and speech difficulties, which often give the false impression that they are mentally impaired.

Diagnosis

The diagnosis of SGBS is based on the presence of certain clinical features and in some cases may be confirmed through **genetic testing**. Not all affected individuals will have all of the features associated with SGBS. SGBS should be considered in an individual who is large in height, weight, and head circumference both before and after birth. Features of the condition that are almost always present include overgrowth; extra nipples; chest deformity; low muscle tone; and characteristic facial features including widely spaced eyes, short nose, large tongue and mouth, central groove of the lower lip, and improperly aligned teeth.

It may be possible to confirm the diagnosis of SGBS through genetic testing. Genetic testing for mutations in the GPC3 gene causing SGB1 is available. Genetic testing involves obtaining a blood sample from the affected individual in order to look for the specific disease-causing mutation in the GPC3 gene. Since not all individuals with SGBS have mutations in the GPC3 gene, it may not be possible to confirm the diagnosis through genetic testing in all individuals suspected of having this condition. Genetic testing for the SGBS can be done on the developing baby before birth through **amniocentesis** or chorionic villus sampling if a mutation in the gene for GPC3 is first identified in an affected family member. Prenatal testing for parents of an affected individual should only be undertaken after the SGBS carrier status of the parents has been confirmed and the couple has been counseled regarding the risks of recurrence.

Treatment and management

The heart function of individuals with SGBS should be carefully monitored because it can be a cause of early death. Individuals with SGBS should be regularly followed by a heart specialist (cardiologist).

Individuals with SGBS are at increased risk to develop kidney tumors. They should be screened for possible kidney tumor development or other tumors of infancy for at least the first five years of life. Screening usually involves an ultrasound (sound wave picture) of the abdomen, including the kidneys.

The large tongue and improperly aligned teeth may lead to speech difficulties. Some individuals may require surgery to reduce the size of the tongue to aid with speech development or for cosmetic reasons. Individuals with speech difficulties may benefit from speech therapy.

Individuals with SGBS may benefit from psychological support and social support to help them reach an adequate level of self-esteem. They may also benefit from **genetic counseling**, which may provide them with further information on the condition itself and recurrence risks for future pregnancies.

Prognosis

The spectrum of clinical manifestations in SGBS is broad, varying from very mild forms in carrier females to

infantile lethal forms in affected males. As many as 50% of males affected with SGBS die in the newborn period. The cause of this high mortality is not known but may be related to heart defects. In one reported family with a severe form of SGBS causing death in the newborn period, the responsible gene was not glypican-3 but the second candidate gene on the X chromosome.

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ORGANIZATIONS

Beckwith-Wiedemann Support Network. 2711 Colony Rd., Ann Arbor, MI 48104. (734) 973-0263 or (800) 837-2976. <http://www.beckwith-wiedemann.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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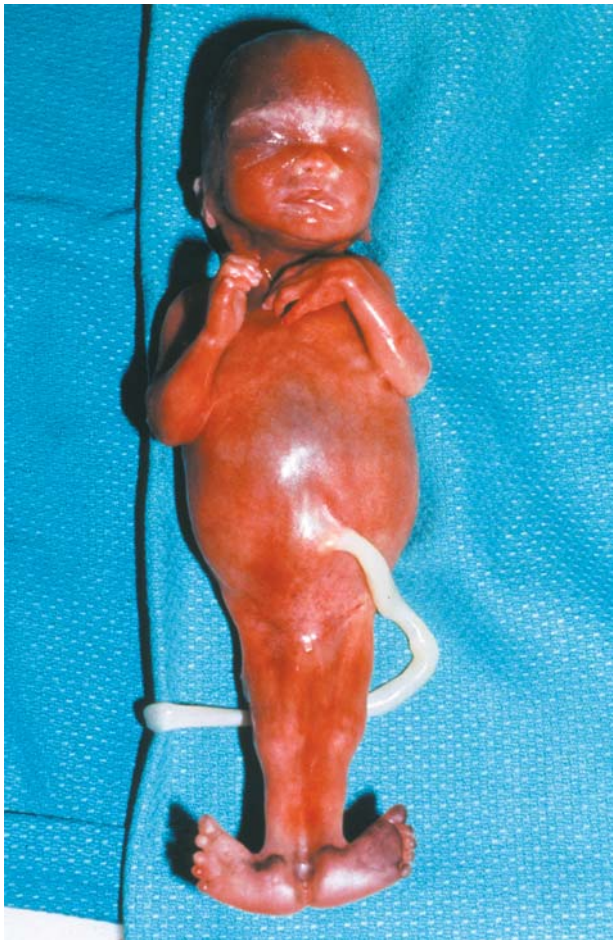
Nada Quercia, MS, CGC, CCGC



Fusion of the lower limbs, such as the legs of this infant, results from vital blood flow and nutrients being diverted away from the lower extremeties due to abnormal umbilical cord blood vessels. *(Greenwood Genetic Center)*

Sirenomelia

Definition

Sirenomelia is a lethal birth defect of the lower body characterized by apparent fusion of the legs into a single lower limb. Other birth defects are always associated with sirenomelia, most commonly abnormalities of the kidneys, large intestines, and genitalia.

Description

This pattern of birth defects is associated with abnormal umbilical cord blood vessels. The normal fetus develops two umbilical arteries, which pump blood from the fetus to the placenta, and one umbilical vein, which returns blood from the placenta to the fetus. The umbilical arteries branch off the iliac arteries in the pelvis. The iliac arteries supply the legs and pelvic organs such as the genitalia. Most babies with sirenomelia have only one umbilical artery and one vein. Rarely a baby with sirenomelia can have the typical two arteries and one vein with occlusion (blockage) of one artery.

In sirenomelia, the one functional artery is larger than normal and branches from the aorta high in the abdomen. Below this umbilical artery, the aorta becomes abnormally narrow. This type of single umbilical artery is known as a vitelline artery because it is thought to arise from the primitive vitelline arteries early in the life of the embryo. The vitelline arteries normally fuse a few weeks after conception to form the arteries that supply the gastrointestinal system and genitourinary system (superior mesenteric, inferior mesenteric, and celiac arteries). If the normal umbilical arteries do not form correctly as branches from the iliac arteries, then a vitelline artery might persist.

KEY TERMS

Aorta—The main artery located above the heart which pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Iliac arteries—Arteries that supply blood to the lower body including the pelvis and legs.

Imperforate anus—Also known as anal atresia. A birth defect in which the opening of the anus is absent or obstructed.

Mermaid syndrome—Alternate name for sirenomelia, often used in older references.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Oligohydramnios—Reduced amount of amniotic fluid. Causes include non-functioning kidneys and premature rupture of membranes. Without amniotic fluid to breathe, a baby will have underdeveloped and immature lungs.

Stillborn—The birth of a baby who has died sometime during the pregnancy or delivery.

Teratogenic—Any agent that can cause birth defects or mental retardation in a developing fetus. Common teratogens are medications or other chemicals but they also include infections, radiation, maternal medical condition, and other agents.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

The vitelline umbilical artery steals blood and nutrition from the lower body and diverts it to the placenta. This results in a small aorta and variable absence of the arteries that supply the kidneys, large intestine, and genitalia (renal, inferior mesenteric, and celiac arteries). Because of the loss of nutrition and blood flow, the lower limbs fail to form as separate limbs, the kidneys do not form or are malformed, the large intestine ends blindly in the abdominal cavity, the anus is imperforate, and the internal and external genitalia are absent or malformed.

The typical malformation of the lower limbs seen in babies with sirenomelia consists of apparent fusion of the legs. There is a spectrum of severity with severe cases having one lower limb that tapers to a point with the absence of foot structures. In these severe cases there are only two bones present in the entire limb (a femur and presumably a tibia). On the mild end of the spectrum are babies with fusion of the skin of the lower limbs only. In these infants the feet may be fully formed with fusion at the ankles. All bones are fully formed and separate. Normally there are three bones in each leg—the femur in the upper leg (thigh) and the tibia and fibula in the lower leg (calf).

Other abnormalities of the upper body involving the heart, lungs, spine, brain, and arms can also be seen in this syndrome, however, not in every affected individual. It is unknown at this time why a single umbilical artery could cause these changes.

Single umbilical artery occurs in about 1% of all liveborn infants. In most of these infants the one umbilical artery is normally formed and not of vitelline origin. In these cases, the risk of other birth defects is low (about 8%). All infants born with a vitelline umbilical artery will have other malformations, the most common being sirenomelia.

Genetic profile

All cases of sirenomelia have occurred in families as isolated cases, and there is no known genetic cause. It is possible that sirenomelia is an autosomal dominant condition and because it is lethal, all cases represent a new mutation. Alternatively, it might be a multifactorial trait where multiple genes and environmental factors come together to cause this pattern of malformations. The fact that all cases have been isolated does not support this possibility. Sirenomelia is more common in twin pregnancies. This may give evidence to an environmental cause.

Demographics

Sirenomelia is rare, estimated to occur once in every 60,000 births. While the exact incidence in different populations is not known, sirenomelia has been reported in a variety of ethnic groups around the world. It is known to be more common in twin pregnancies and in babies born to mothers with **diabetes mellitus**.

Signs and symptoms

Abnormalities associated with sirenomelia include:

- absence of the kidneys or malformed non-functioning kidneys
- blind ending colon and imperforate anus
- small, absent, fused, or poorly formed pelvic bones
- small, absent, or poorly formed internal and external genitalia

- fusion of the lower limbs along the inner leg, from skin only to complete fusion with the appearance of only one leg
- death from underdeveloped and immature lungs caused by oligohydramnios
- birth defects in the upper body sometimes occur and include abnormalities in the heart, lungs, arms, spine, and brain

Diagnosis

The diagnosis is obvious at birth on examination of a baby, but prenatal diagnosis often occurs in the second trimester (weeks 13 through 26 of a pregnancy) by an ultrasound.

Treatment and management

Babies born alive with functioning kidneys may survive with appropriate surgical management. Operations to reconstruct the urinary and gastrointestinal outlet tracts are almost always needed. Other procedures and treatments depend of the extent of other birth defects. It appears that if a baby does survive, he or she will not have any mental delays.

Prognosis

Because of the birth defects involving the gastrointestinal tract and kidneys, sirenomelia is almost always fatal. About 50% of babies are stillborn (the baby has died before delivery) and 50% are liveborn with survival lasting a few minutes to a few days. There have been at least two reported cases of sirenomelia that have survived beyond the first month of life. These infants had normal functioning kidneys during their development.

Resources

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Randall Stuart Colby, MD

Sjögren-Larsson syndrome

Definition

Sjögren-Larsson syndrome is an inherited disorder characterized by **ichthyosis** (scaly skin), speech abnormalities, mental retardation, and spasticity (a state of increased muscle tone with heightened reflexes). Severity is variable.

Description

Sjögren-Larsson syndrome is a rare genetic disorder inherited in an autosomal recessive fashion. First characterized by Swedish psychiatrist Torsten Sjögren in 1956 (and by Sjögren and Tage Larsson in 1957), they suggested that all Swedes with the syndrome are descended from one ancestor in whom a mutation (a genetic change) occurred about 600 years ago. The highest incidence of the disease occurs in northern Sweden.

In infancy, development of various degrees of scaling and reddened skin occurs, often accompanied by hyperkeratosis (thickening of the skin) on the outer skin layer. After infancy, skin on the arms, legs and abdomen often is dark, scaly, and lacking redness. Seizures and speech abnormalities may accompany skin symptoms. About half of children affected with the syndrome experience degeneration of the pigment in the retina of the eye.

Sjögren-Larsson syndrome is also sometimes known as SLS; congenital ichthyosis-mental retardation-spasticity syndrome; ichthyosis-spastic neurologic disorder-oligophrenia syndrome; fatty aldehyde dehydrogenase deficiency (FALDH deficiency); fatty aldehyde dehydrogenase 10 deficiency (FALDH10 deficiency); or disorder of cornification 10 (Sjögren-Larsson Type). Sjögren-Larsson syndrome is not to be confused with Sjögren syndrome; it is sometimes called the T. Sjögren syndrome to distinguish it from Sjögren syndrome (characterized by dry eyes and mouth), which was described by Swedish ophthalmologist Henrick Sjögren.

Genetic profile

Inheritance of Sjögren-Larsson syndrome is autosomal recessive. In autosomal recessive inheritance, a single abnormal **gene** on one of the autosomal **chromosomes** (one of the first 22 "non-sex" chromosomes) from both parents can cause the disease. Both of the parents must be carriers in order for the child to inherit the disease since recessive genes are expressed only when both copies in the pair have the same recessive instruction. Neither of the parents has the disease (since it is recessive).

KEY TERMS

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Diplegia—Paralysis affecting like parts on both sides of the body, such as both arms or both legs.

Hypertonia—Excessive muscle tone or tension, causing resistance of muscle to being stretched.

Ichthyosis—Rough, dry, scaly skin that forms as a result of a defect in skin formation.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Tetraplegia—Paralysis of all four limbs. Also called quadriplegia.

A child with both parents who carry the disease has a 25% chance having the disease; a 50% chance of being a carrier of the disease (but not affected by the disease, having both one normal gene and one gene with the mutation for the disorder); and a 25% chance of receiving both normal genes, one from each parent, and being genetically normal for that particular trait.

The gene for the Sjögren-Larsson syndrome, FALDH, is located on chromosome number 17 in band 17p11.2. The **gene mutation** that is responsible for the disorder is located near the center of the chromosome and is strongly associated the gene markers called D17S805 and ALDH10.

Demographics

Sjögren-Larsson syndrome is a rare disorder. The highest incidence occurs in northern Sweden. The mutation responsible for the disease is present in approximately 1% of the population in northern Sweden. All Swedes with the syndrome are believed to be descendents of one ancestor in whom a genetic change occurred about 600 years ago. (The phenomenon wherein everyone is descended from one person within what was once a tiny group of people is called founder effect.) The disease also occurs in members of families of other European, Arabic, and native American descent, but is less prevalent. Sjögren-Larsson syndrome affects both males and females.

Signs and symptoms

There are several signs and symptoms of Sjögren-Larsson syndrome. The major features of the disorder are the following:

- Skin: In infancy, development of various degrees of scaling and reddened skin occurs (ichthyosis), often accompanied by hyperkeratosis (thickening of the skin) on the outer skin layer. After infancy, skin on the arms, legs, and abdomen is often dark and scaly and lacking redness. Bruises are present at birth or soon after.
- Hair: Hair may be brittle.
- Extremities: Joint contracture and hypertonia cause resistance of joints to movement and of muscles to stretching. Most individuals with the syndrome never walk.
- Eyes: About half of the individuals with this syndrome have **retinitis pigmentosa** (pigmentary degeneration of the retina). Glistening white or yellow-white dots on the retina (ocular fundus) are characteristic. They may be an early sign of the disease, presenting at age 1–2, and may increase with age.
- Nervous system: Spastic diplegia or tetraplegia (paralysis) affecting arms and/or legs. About half of the individuals with this disorder have seizures.
- Urogenital system: Kidney diseases may be associated with this syndrome.
- Growth and development: Individuals with the disorder tend to be unusually short in stature. Mental retardation is characteristic. Speech disorders may be present.

Speech abnormalities, mental retardation, and seizures usually occur during the first two or three years of life.

Diagnosis

The clinical features of Sjögren-Larsson syndrome are often distinctive, and a pattern of anomalies may suggest the diagnosis. In addition to ichthyosis and spasticity at birth, glistening white or yellow-white dots on the retina may be an early sign of the disease, presenting in the first or second year of life. If they occur, speech abnormalities, mental retardation, and seizures present during the first two or three years of life.

Laboratory findings are important in diagnosing Sjögren-Larsson syndrome. A laboratory test for deficiency of an enzyme (a protein that catalyzes chemical reactions in the human body) called fatty aldehyde dehydrogenase 10 (FALDH10) will determine presence of the disease. Sjögren-Larsson is due to a deficiency of FALDH10, and the gene for the Sjögren-Larsson syndrome is the same as the FALDH10 gene.

Positive laboratory results for Sjögren-Larsson will include the following findings:

- Hexadeconal elevated in fibroblasts.
- Fatty alcohol NAD+ deficient in Sjögren-Larsson syndrome fibroblasts.
- Fatty aldehyde dehydrogenase (FALDH) deficiency.

Genetic counseling

Individuals with a family history of Sjögren-Larsson syndrome may benefit from **genetic counseling** to learn about the condition including treatments, inheritance, testing, and options available to them so that they can make informed decisions appropriate to their families. A child with both parents who carry the Sjögren-Larsson gene mutation has a 25% chance having the disorder. Couples who have had one affected child have a 25% risk of having another child with the disorder in each pregnancy.

Prenatal testing

Families at risk to have a child with Sjögren-Larsson syndrome may have the option of prenatal diagnosis. **DNA** can be extracted from fetal cells obtained by either chorionic villus sampling (usually done until 12 weeks gestation) or **amniocentesis** (usually done at 16–18 weeks gestation) and tested to determine if the altered gene in the family is present. These techniques usually require that the alteration in the gene has been identified previously in an affected family member.

Chorionic villus sampling is a procedure to obtain chorionic villi tissue for testing. Chorionic villi are microscopic, finger-like projections that emerge from the chorionic membrane and eventually form the placenta. The cells of the chorionic villi are of fetal origin so laboratory analysis can identify a number of genetic abnormalities of the fetus. Because the villi are attached to the uterus, however, there is a chance that maternal tissue may be analyzed rather than the fetal cells. If the sample is too small, it may be necessary to repeat the procedure. In addition, the quality of the chromosome analysis is usually not as good with chorionic villus sampling as with amniocentesis. The chromosomes may not be as long, and so it may not be possible to identify some of the smaller bands on the chromosomes.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus, into the amniotic sac, and withdrawing a small amount of amniotic fluid (a liquid produced by the fetal membranes and the fetus that surrounds the fetus throughout pregnancy). DNA can be extracted from the fetal cells contained in the amniotic fluid and tested for the specific mutation known to cause Sjögren-Larsson syndrome.

Treatment and management

Individuals with Sjögren-Larsson syndrome should be under routine health supervision by a physician who is familiar with the disorder, its complications, and its treatment. Supportive resources for individuals with Sjögren-Larsson syndrome and their families should be provided. Some clinical improvement has been reported to occur with fat restriction in the diet and supplementation with medium-chain triglycerides.

Other treatment of the disorder is generally symptomatic.

- For dermatologic symptoms, various skin softening ointments are useful in reducing symptoms. Plain petroleum jelly may be effective, especially when applied while the skin is still moist, such as after bathing. Salicylic acid gel may also be effective. When using the ointment, skin is covered at night with an airtight, waterproof dressing. Lactate lotion is another effective treatment for the dermatologic symptoms.
- For ocular symptoms, regular care from a qualified opthamologist is important.
- To control seizures, anti-convulsant medications may be helpful.
- Speech therapy and special education services may be helpful.

Prognosis

Prognosis is variable depending upon the severity of the disease. Sjögren-Larsson does not generally lead to shortened life span.

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Willemsen, M.A., et al. “Sjögren-Larsson Syndrome.” *Journal of Pediatrics* 136(February 2000): 261.

ORGANIZATIONS

Arc (a National Organization on Mental Retardation). 1010 Wayne Ave., Suite 650, Silver Spring, MD 20910. (800) 433-5255. <http://www.thearclink.org>.

Foundation for Ichthyosis and Related Skin Types. 650 N. Cannon Ave., Suite 17, Landsdale, PA 19446. (215) 631-1411 or (800) 545-3286. Fax: (215) 631-1413. <http://www.scalyskin.org>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases. National Institutes of Health, One AMS Circle, Bethesda, MD 20892. <http://www.nih.gov/niams>.

WEBSITES

Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?db=OMIM>.

Jennifer F. Wilson, MS

Skeletal dysplasia *see* **Larsen syndrome**

Sly syndrome (MPS VII) *see* **Mucopolysaccharidosis (MPS)**

Smith syndrome *see* **Smith-Lemli-Opitz syndrome**

Smith-Fineman-Myers syndrome

Definition

Smith-Fineman-Myers syndrome (SFMS) is a rare and severe type of X-linked inherited mental retardation.

Description

Smith-Fineman-Myers syndrome is also known as Smith-Fineman-Myers type mental retardation and Smith-Fineman-Myers type X-linked mental retardation. SFMS results in severe mental retardation along with characteristic facial features and skeletal differences.

Genetic profile

Smith-Fineman-Myers syndrome is an X-linked disease. X-linked diseases map to the human X chromosome, a sex chromosome. Females have two X **chromosomes**, whereas males have one X chromosome and one Y chromosome. Because males have only one X chromosome, they require only one copy of an abnormal X-linked **gene** to display disease. Because females have two X chromosomes, the effect of one X-linked recessive disease gene is masked by the disease gene's normal counterpart on her other X chromosome.

In classic X-linked **inheritance** males are affected, presenting full clinical symptoms of the disease. Females are not affected. Affected fathers can never pass X-linked diseases to their sons. However, affected fathers always pass X-linked disease genes to their daughters. Females who inherit the faulty gene but do not show the disease are known as carriers. Female carriers of SFMS have a 50% chance to pass the disease-causing gene to each of their children. Each of a female carrier's sons has a 50% chance to display the symptoms of SFMS. None of a female carrier's daughters would display symptoms of SFMS.

Some patients with SFMS have been found to have a mutation in the ATRX gene, on the X chromosome at a location designated as Xq13. ATRX is also the disease gene for several other forms of X-linked mental retardation. Mutations in ATRX are associated with X-linked Alpha-thalassemia/mental retardation syndrome, **Carpenter syndrome**, Juberg-Marsidi syndrome, and X-linked mental retardation with spastic paraplegia. It is possible that some patients with SFMS have X-linked Alpha-thalassemia/mental retardation syndrome without the hemoglobin H effects that lead to Alpha-thalassemia in the traditionally recognized disease.

Demographics

SFMS affects only males and is very rare. As of early 2001, only 12 cases have been reported in the medical literature. SFMS has been reported in brothers of affected boys.

Signs and symptoms

SFMS visibly affects the skeletal and nervous systems and results in an unusual facial appearance. The genitals may also show effects ranging from mild (e.g. undescended testes) to severe (leading to female gender assignment).

Skeletal features

Boys with SFMS have short stature and a thin body build. Their heads are small and may also be unusually shaped. **Scoliosis** and chest abnormalities have been reported to occur with SFMS. X rays may show that their bones have characteristics of the bones of people younger than they are. Hands are often short with unusual palm creases and short, unusually shaped fingers. Fingernails may be abnormal. Foot abnormalities and shortened or fused toes have also been reported.

Neurological features

Boys with SFMS exhibit severe mental retardation. Restlessness, behavior problems, seizures, and severe delay in language development are common. Boys with SFMS may be self-absorbed with reduced ability to socialize with others. Affected boys show reduced mus-

KEY TERMS

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Tone—A term used to describe the tension of muscles. Increased tone is increased tension in the muscles.

cle tone as infants and young children. Later, muscle tone and reflexes are abnormally increased causing spasticity.

Boys with SFMS may display cortical atrophy, or degeneration of the brain's outer layer, on brain imaging studies. Cortical atrophy is commonly found in older unaffected people. When cortical atrophy is found in younger people it is typically due to a serious brain injury. Brain biopsies of two patients with SFMS have been normal.

Facial features

SFMS is associated with unusual facial features including a large mouth with a drooping lower lip, prominent upper jaw and front teeth, and an underdeveloped chin. Cleft palate has been reported in one set of affected twins. Eyes are widely spaced with drooping eyelids. Skin may be lightly pigmented with multiple freckles.

Diagnosis

Assessment for any type of mental retardation should include a detailed family history and thorough physical exam. Brain and skeletal imaging through CT scans or x rays may be helpful. A chromosome study and certain other genetic and biochemical tests help to rule out other possible causes of mental retardation.

Diagnosis of SFMS has traditionally been based on the visible and measurable symptoms of the disease. Until 2000, SFMS was not known to be associated with any particular gene. As of 2001, scientists do not yet know if other genes may be involved in some cases of this rare disease. Genetic analysis of the ATRX gene may, however, prove to be helpful in diagnosis of SFMS.

Treatment and management

Treatment for SFMS is based on the symptoms each individual displays. Seizures are controlled with anticonvulsants. Medications and behavioral modification routines may help to control behavioral problems.

Prognosis

Retardation is severe, but it does not seem to get worse with age. Lifespan does not appear to be shortened.

Resources

BOOKS

Carlson, Hannah, et al. *I Have a Friend Who Has Mental Retardation.* Madison, CT: Bick Publishing House, 1997.

Shannon, Joyce Brennfleck. *Mental Retardation SourceBook: Basic Consumer Health Information about Mental Retardation and Its Causes, Including Down Syndrome, Fetal Alcohol Syndrome, Fragile X Syndrome.* Detroit: Omnigraphics, Inc., 1999.

ORGANIZATIONS

American Association on Mental Retardation (AAMR). 444 North Capitol Street NW, Suite 846, Washington, DC 20001-1512. (800) 424- 3688. <http://www.aamr.org>.

Arc of the United States (formerly Association for Retarded Citizens of the US). 500 East Border St., Suite 300, Arlington, TX 76010. (817) 261-6003. <http://thearc.org>.

WEBSITES

GeneClinics. <http://www.geneclinics.org>.

Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>.

Judy C. Hawkins, MS

Smith-Fineman-Myers type X-linked mental retardation *see* **Smith-Fineman-Myers syndrome**

Smith-Lemli-Opitz syndrome

Definition

Smith-Lemli-Opitz syndrome (SLOS) is a syndrome characterized by microcephaly (small head size), mental retardation, short stature, and major and minor malformations. It is caused by an abnormality in cholesterol metabolism.

Description

SLOS was first characterized by David W. Smith, John M. Opitz, and Luc Lemli in 1964. The syndrome has variable characteristics marked mainly by short stature, mental retardation, microcephaly, postaxial polydactyly (an extra digit on the little finger side of the hand or the little toe side of the foot), cleft palate, cardiovascular defects, genital malformations and other abnormalities associated with abnormal cholesterol metabolism. In 1993, scientists discovered that children with SLOS have a metabolic disorder that prevents cholesterol from being made in amounts sufficient for normal growth and development.

KEY TERMS

Anomaly—Different from the normal or expected. Unusual or irregular structure.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Congenital—Refers to a disorder which is present at birth.

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Hypotonia—Reduced or diminished muscle tone.

Microcephaly—An abnormally small head.

Polydactyly—The presence of extra fingers or toes.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

Syndactyly—Webbing or fusion between the fingers or toes.

Sometimes the severe form of the disease is called SLOS type II. But laboratory testing has shown that type II is not biochemically distinct. Rather it represents the more severe expression of the SLOS phenotype.

SLOS is also known as Smith syndrome, RSH syndrome, and RSH/Smith-Lemli-Opitz (RSH/SLO) syndrome. The designation RSH represents initials of the surnames of the first three patients in whom the syndrome was first observed.

Genetic profile

SLOS is inherited in an autosomal recessive manner. In autosomal recessive **inheritance**, a single abnormal **gene** on one of the autosomal **chromosomes** (one of the first 22 "non-sex" chromosomes) from both parents can cause the disease. Both of the parents must be carriers in order for the child to inherit the disease since recessive genes are expressed only when both copies in the pair have the same recessive instruction. Neither of the parents has the disease (since it is recessive).

A child with both parents who carry the disease has a 25% chance having the disease; a 50% chance of being a carrier of the disease (having both one normal gene and one gene with the mutation for the disorder) but not affected by the disease; and a 25% chance of receiving both normal genes, one from each parent, and being genetically normal for that particular trait.

The gene for SLOS, DHCR7, encodes 7-dehydrocholesterol (7-DHC) reductase, the enzyme that is deficient in SLOS. DHCR7 is on the long arm of chromosome 11 at locus 11q12-q13.

Demographics

SLOS occurs in approximately one in 20,000 to 30,000 births in populations of northern and central European background. Evidence suggests that there is a higher frequency of SLOS in people of northern European ancestry and a lower frequency in people of Asian or African background.

Because of the presence of recognizable genital abnormalities, males are more likely than females to be evaluated for a diagnosis of SLOS. Therefore, the occurrence of the disease among females is less certain.

Signs and symptoms

The following are features of the congenital multiple anomaly syndrome.

- Nearly 90% of people with SLOS have microcephaly.
- Nearly all people with SLOS have moderate to severe mental retardation.
- Other neurologic findings are less common. These include seizures and muscle hypotonia.
- Characteristic facial features include narrowing at the temples, epicanthal folds (skin fold of the upper eyelid covering the inner corner of the eye), downslanting eyes, drooping upper eyelids, anteverted nares (nostrils that tilt forward), and abnormal smallness of the jaw (micrognathia). Cleft palate is present in 40–50% of people with SLOS, and about 20% have congenital cataracts. Strabismus, poor tracking, opsoclonus (impairment of eye movements), and optic nerve demyelination (deterioration) are other possible ophthalmologic manifestations.
- Cardiac abnormalities are present in about 35–40% of patients with SLOS. Increased incidence of atrioventricular canal defects and anomalous pulmonary venous return is seen in people with SLOS.
- Urogenital anomalies are frequent. Kidney hypoplasia (smaller than normal) or **dysplasia** (abnormal development) occurs in about 40% of people with SLOS. Genital anomalies of variable severity may include hypospadias and/or bilateral cryptorchidism, which occur in about half of reported cases, and small penis.

Many 46,XY individuals with severe manifestations of SLOS have undermasculinization of the external genitalia, resulting in female external genitalia (sex reversal). Abnormalities in the uterus and vagina have been noted in 46,XX females.

- Syndactyly of the second and third toes occurs frequently. Postaxial polydactyly is present in 25–50% of all cases. Other abnormalities affecting the hands and feet may be present.
- Short stature is common. Limbs and neck are shorter than normal.

In addition, a child with SLOS will often show failure to thrive, have abnormal sleep patterns, and have photosensitivity. The hair of children with SLOS is blonde.

Growth may be retarded prenatally. Neonates frequently have poor suck, irritability, and failure to thrive.

Diagnosis

The clinical features of SLOS are often distinctive, and a pattern of congenital anomalies suggests the diagnosis. Features that are most commonly seen are microcephaly, postaxial polydactyly, 2–3 syndactyly of the toes, growth and mental retardation, cleft palate, and hypospadias in males.

The diagnosis of SLOS relies on clinical suspicion and detection of abnormally elevated serum concentration of 7-dehydrocholesterol (7-DHC) or an elevated 7-dehydrocholesterol:cholesterol ratio. Serum concentration of cholesterol is usually low, with cholesterol levels less than 50 mg/dl (normal is greater than 100 mg/dl). Cholesterol is an essential building block of all cell membranes and the white matter of the brain, and SLOS appears to be caused by abnormally low levels of the enzyme 7-DHC-reductase, which converts 7-DHC into cholesterol. Children with SLOS with the lowest cholesterol levels tend to have the most severe forms of the disorder and often die at birth or in the first few months. In about 10% of patients, cholesterol is in the normal range, so it is an unreliable marker for screening and diagnosis.

Molecular **genetic testing** of the DHCR7 gene is not generally available. But since the molecular structure of the DHCR7 has been identified, the possibility now exists for DNA-based testing for diagnosis and **genetic counseling**. Currently, such testing is available on a research basis only.

Genetic counseling

Carrier detection is problematic using biochemical testing. In carriers, 7-DHC and cholesterol levels are usually normal. Carrier testing is now possible, although not generally available, by measurement of 7DHC or enzyme levels in cultured cells. More accurate DNA testing for DHCR7 mutations is not currently available, but it is anticipated in the near future. Couples who have had one affected child have a 25% risk of having a child with SLOS in each pregnancy.

Prenatal testing

For couples known to be at 25% risk for having a baby with SLOS, testing is available to assist in prenatal diagnosis. Prior testing of family members is usually necessary for prenatal testing.

Either chorionic villus sampling (CVS) or **amniocentesis** may be performed for prenatal testing. CVS is a procedure to obtain chorionic villi tissue for testing. Abnormal levels of 7-dehydrocholesterol in amniotic fluid or chorionic villus samples is diagnostic of SLOS. Chorionic villus sampling can be performed at 10–12 weeks gestation.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus, into the amniotic sac, and withdrawing a small amount of amniotic fluid. SLOS can be diagnosed from biochemical testing performed on the amniotic fluid. DNA can also be extracted from the fetal cells contained in the amniotic fluid and tested. Amniocentesis is performed at 16–18 weeks gestation.

Abnormal concentration of 7-dehydrocholesterol levels in tissue obtained from CVS or in amniotic fluid is diagnostic.

For low-risk pregnancies, in which there is no family history of SLOS, certain findings in the fetus might prompt consideration of SLOS. The combination of low unconjugated estriol levels, low HCG, and low alpha-fetoprotein on routine maternal serum testing at 16–18 weeks gestation might suggest the possible diagnosis of SLOS. Findings on ultrasound examination such as cardiac defects, cleft palate, genital abnormalities, or growth retardation might be suggestive, prompting consideration of a 7-dehydrocholesterol assay of amniotic fluid.

Low uE3 levels alone may be an indication of further investigation, especially if it is associated with abnormal ultrasonographic findings suggestive of SLOS.

Treatment and management

It is not known what role the elevated levels of 7-DHC and other sterol precursors—not usually present in significant concentrations in the plasma—play in the pathogenesis of SLOS. Children with SLOS should be under routine health supervision by a physician who is familiar with SLOS, its complications, and its treatment.

Since a common complication of the syndrome is pneumonia, it should be treated with appropriate antibiotics when it occurs.

Special education services and physical therapy may be recommended as needed.

Infant care

A physician familiar with the range of problems seen in infants with SLOS is important for appropriate health supervision and anticipatory guidance. Poor feeding and problems with weight gain are common in infants with SLOS. Many infants have difficulties with suck and/or swallow and may require alternative feeding. A diagnosis of **pyloric stenosis** (caused by a thickening and spasm of the stomach outlet) should be considered for those with frequent vomiting or apparent gastroesophageal reflux. Particular attention should also be given to the stooling pattern, abdominal distention, or other signs of possible obstruction, particularly in children with more severe phenotype, since these may indicate **Hirschsprung disease** (absent nerves in colon).

Surgical treatment

Surgical management of congenital anomalies such as cleft palate, congenital heart disease, and genital anomalies for the more severely affected infants need to be considered as they would in any other infant with a severe, usually lethal disorder. Even with vigorous intervention, children with multiple major manifestations of SLOS are believed to have decreased survival. Reassignment of sex of rearing for 46,XY infants with female genitalia may not always be appropriate because most will have early death. The process of gender reassignment can be disruptive to a family already coping with the difficult issues of having a child with a genetic disorder that has life-threatening medical complications.

Dietary supplementation

Because SLOS is a cholesterol deficiency syndrome, research trials have recently included dietary cholesterol supplementation. An increase in total caloric intake and an increase in cholesterol intake hold promise for treatment of SLOS, but the research is still preliminary. Benefits reported in preliminary studies include improved growth in children with SLOS, possible enhanced developmental progress, reduced dermatologic problems (rashes, photosensitivity), and improved behavior. No harmful side effects of cholesterol supplementation have been documented.

Prognosis

Prognosis is variable depending upon the severity of the disease. Children with SLOS who have multiple major malformations are believed to have decreased survival, even with vigorous intervention.

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ORGANIZATIONS

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Smith-Lemli-Opitz Advocacy and Exchange (RSH/SLO). 2650 Valley Forge Dr., Boothwyn, PA 19061. (610) 485-9663. <http://members.aol.com/slo97/index.html>.

WEBSITES

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Jennifer F. Wilson, MS

Smith-Magenis chromosome region *see* **Smith-Magenis syndrome**

Smith-Magenis syndrome

Definition

Smith-Magenis syndrome (SMS) is a relatively rare genetic disorder characterized by a specific pattern of physical, behavioral, and developmental features. First described in 1982 by Ann C.M. Smith (a genetics counselor) and Ellen Magenis (a physician and chromosome expert), the syndrome results from a deletion on chromosome 17, specifically referred to as deletion 17p11.2.

Description

Until the mid 1990s, SMS was not a well-known disorder, even among genetics experts; the chromosome deletion is small (a microdeletion) and difficult to detect. Most

individuals are not diagnosed until they receive specialized genetic tests, usually in mid-childhood or adulthood.

Smith-Magenis syndrome causes multiple birth defects (congenital abnormalities) as well as moderate to severe mental retardation. The clinical manifestations of SMS vary. However, a number of characteristic physical features, developmental delays, and behavioral problems occur in all patients with the disorder. According to some researchers, the extent of the chromosomal deletion may account for the variable severity of symptoms.

The most common and clinically recognizable features of those with SMS include mild to moderate brachycephaly (short, wide head), flat mid-face, mental retardation, and short, broad hands. Common but less consistent physical abnormalities include prominent forehead, protruding jaw, and low-set ears. The major clinical features and the specific abnormalities of SMS are the most obvious diagnostic clues to the disorder. Some experts believe that with more research on this syndrome, SMS may be determined to be a relatively common cause of mental retardation.

Genetic profile

Although SMS is caused by a deletion of genetic material from a portion of chromosome 17, the syndrome usually does not run in families. In most cases, the deletion occurs accidentally at conception when an abnormal sperm or egg from one parent unites with a normal sperm or egg from the other parent. The abnormal sperm or egg contains the missing chromosomal material. These abnormal sperm or eggs are present in everyone; however, the risk of an abnormal conception increases significantly with the parents' ages.

Research has shown a random parental origin of deletion, suggesting that SMS is likely a contiguous **gene** deletion syndrome. Continguous gene syndromes are conditions that occur as a result of microdeletions or microduplications involving several neighboring genes.

Demographics

Although the exact incidence of SMS is not known, the disorder is rare and estimated to occur in approximately one in 25,000-50,000 live births. Only about 150 cases have been identified worldwide from a diversity of ethnic groups. The ages of those affected ranges from neonates to individuals in their 70s. About an equal number of males and females are affected by the disorder.

Signs and symptoms

Although there are many features associated with SMS, not every individual exhibits all of these features. The following is a common list of traits that have been reported:

- Distinct facial features: brachycephaly, flat mid-face area, prominent forehead, eyelid folds, broad nasal bridge, protruding jaw, and low-set ears
- Brachydactyly (short fingers and toes)
- Short stature
- Hoarse, deep voice
- Speech delay
- Learning disabilities
- Chronic ear infections
- Mental retardation (typically in the 50-60 range for I.Q.)
- Poor muscle tone and/or feeding problems in infancy
- Eye disorders
- Sleep disturbances
- Insensitivity to pain

KEY TERMS

Brachycephaly—An abnormal thickening and widening of the skull.

Brachydactyly—Abnormal shortness of the fingers and toes.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Continguous gene syndrome—Conditions that occur as a result of microdeletions or microduplications involving several neighboring genes.

FISH (fluorescence *in situ* hybridization)—Technique used to detect small deletions or rearrangements in chromosomes by attempting to attach a fluorescent (glowing) piece of a chromosome to a sample of cells obtained from a patient.

Melatonin—A sleep-inducing hormone secreted by the pineal gland.

Phenotype—The physical expression of an individuals genes.

Scoliosis—An abnormal, side-to-side curvature of the spine.

- Behavioral problems: hyperactivity, head banging, hand/nail biting, skin picking, pulling off fingernails and toenails, explosive outbursts, tantrums, destructive and aggressive behavior, excitability, arm hugging/squeezing when excited
- Engaging and endearing personality

Less common symptoms include:

- Heart defects
- **Scoliosis** (curvature of the spine)
- Seizures
- Urinary tract abnormalities
- Abnormalities of the palate, cleft lip
- Hearing impairment

Diagnosis

Although SMS is generally believed to be underdiagnosed, with increased professional awareness and improved methods of testing, the number of individuals identified increases annually. In diagnosing the disorder, the characteristic behavioral features of SMS are usually recognized before the facial features, often leading to a delay in diagnosis.

Phenotype (physical features) identification

Facial abnormalities evolve over time and are more subtle in early childhood. Thus, diagnosis of SMS at birth or in infancy is infrequent and is usually made by chance when abnormal facial features suggest a diagnosis of **Down syndrome** (a more commonly known congenital abnormality caused by an extra chromosome 21) and chromosome testing reveals the SMS 17p11.2 deletion.

The phenotypic overlap of SMS with Down syndrome, particularly in early life, can be striking. Both conditions share a number of features, including brachycephaly, upward-slanting eyes, a short and broad nose, mid-face flattening, eye disorders, short stature, small hands and feet, and poor muscle tone. However, age evolves the somewhat coarse appearance of the face, and by young adulthood, the phenotype of the disorder is well developed and striking. Familiarity with the clinical manifestations of both **genetic disorders** improves the likelihood of early diagnosis and intervention.

High resolution chromosome analysis

The diagnosis of SMS is often confirmed through a blood test called a high resolution chromosome analysis, which is generally performed for the evaluation of developmental delays or congenital abnormalities. In the case of microdeletions, the chromosome deletions are so small that often they cannot be detected by chromosome analysis alone. In the older child, however, the phenotype is distinctive enough for a clinical diagnosis to be made by an experienced clinician prior to the chromosome analysis.

FISH analysis

If chromosome analysis is inconclusive, FISH (fluorescence *in situ* hybridization) is the test of choice to document the SMS deletion because its high degree of accuracy. In FISH analysis, which has become a standard molecular test, denatured **DNA** (DNA altered by a process that separates the complimentary strands within the DNA double helix structure) is kept in place in the chromosome and is then hybridized (mixed) with **RNA** or DNA (extracted from another source) to which a fluorescent tag has been attached. The advantage of maintaining the DNA in the chromosome is that the specific chromosome (or **chromosomes**) containing the gene of interest can be identified by observing, under a microscope, the location of the fluorescence. Combining FISH and standard chromosome analysis can characterize the structural rearrangements and marker chromosomes.

In SMS, predictive or prenatal screening is an unlikely outcome of identifying the flawed gene because the disease is so rare and does not run in families. Instead, researchers hope to determine how the extent of the microdeletion on chromosome 17 is related to the various signs and symptoms of SMS.

Treatment and management

There is no cure for SMS because the disorder is so complex and has received relatively little research attention. Therefore, managing symptoms becomes a priority in those diagnosed with the disorder.

A child with SMS typically displays self-injurious behavior as well as attention-seeking outbursts and aggressive behavior. Medications such as carbamazapine (an anticonvulsant) may be prescribed for severe behavioral problems associated with SMS. However, in most cases, drugs to help control or modify behavior or increase attention span have been found to be minimally effective. Any pharmacologic treatment of SMS remains individual, and several drugs may need to be tested to optimize results.

In addition to behavioral problems, children with SMS tend to have speech delays. Therefore, speech therapy, starting as early as possible, is typically beneficial. Most children learn to communicate verbally, either with sign language or gestures.

Since children with SMS are often easily distracted, they tend to do better in small, focused classroom set-

tings in which there are no more than five to seven children. If the classroom is larger, competition for the teacher's attention increases, along with the probability of behavioral problems. These children also seem to respond to consistency, structure, and routines; changes in routine can provoke behavioral outbursts and tantrums.

Children with SMS have problems with sequential processing, which makes counting, mathematical skills, and multi-step tasks especially difficult. They tend to learn best with visual cues (such as pictures illustrating tasks). Also, since they have a fascination with electronics, the use of computers and other technology may be effective teaching tools in these children. Generally very responsive to affection, praise, and other positive emotions, children with SMS usually enjoy interacting with adults. A parent or teacher's positive response can often motivate a child to learn.

More than half of children with SMS have sleep disturbances such as daytime sleepiness, difficulty falling asleep at night, nocturnal awakening, decreased sleep time, and abnormalities in REM (rapid eye movement) sleep. These disturbances are due to abnormal melatonin metabolism. Melatonin is a sleep-inducing hormone secreted by the pineal gland in the brain. Therefore, a locking mechanism on the door may be helpful in preventing the child from wandering out of his or her bedroom at night. Also, a night-time dose of melatonin has been recommended for some children and adults with SMS.

Some experts have suggested that every individual with SMS have annual examinations for thyroid function, scoliosis, and eye problems. If any of these tests is abnormal, intervention and further clinical evaluation is appropriate.

Prognosis

Although there is no medical prevention or cure for SMS, early diagnosis gives parents time to learn about and prepare for the challenges of the disease. Although there is insufficient data regarding the average life expectancy of those diagnosed with SMS, some individuals have lived well into their 70s.

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WEBSITES

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Smith-Magenis Mailing List. <http://www.egroups.com/group/sms-list>.

Special Child: For Parents of Children With Disabilities. <http://www.specialchild.com>.

Genevieve T. Slomski, PhD

Sotos syndrome

Definition

Sotos syndrome is a genetic condition causing excessive growth and a distinctive head and facial appearance. It has in the past been known as cerebral gigantism. It is often accompanied by delayed development, low muscle tone, and impaired speech.

Description

Sotos syndrome was first described in 1964 and is primarily classified as an overgrowth syndrome, which means that the individual affected with it experiences rapid growth. A number of different symptoms occur in Sotos syndrome, however, it primarily results in rapid growth beginning in the prenatal period and continuing through the infancy and toddler years and into the elementary school years. It is also strongly associated with the bones developing and maturing more quickly (advanced bone age), in a distinctive appearing face, and in developmental delay.

The excessive prenatal growth often results in the newborn being large with respect to length and head circumference; weight is usually average. The rapid growth continues through infancy and into the youth years with the child's length/height and head circumference often being above the 97th percentile, meaning that out of 100 children of the same age, the child is longer/taller and has a larger head than 97 of the children. The rate of growth

KEY TERMS

Advanced bone age—The bones, on x ray, appear to be those of an older individual.

Congenital—Refers to a disorder which is present at birth.

Failure to thrive—Significantly reduced or delayed physical growth.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

appears to decrease in later childhood and adolescence and final heights tend to be within the normal ranges.

The facial features of individuals with Sotos syndrome change over time. In infants and toddlers, the face is round with the forehead being prominent and the chin small. As the child grows older and becomes an adolescent, the face becomes long with the chin being more prominent, usually with a pointed or square shape. In adults, faces are usually long and thin. The head remains large from birth through adulthood.

Hypotonia is present at birth in nearly every child with Sotos syndrome. Hypotonia means that there is significantly less tone in the muscles. Bodies with hypotonia are sometimes referred to as “floppy”. Muscle tone improves as the child grows older but even in adults, it is still present to some degree. Hypotonia affects many aspects of the baby’s development. It can cause difficulty in sucking and swallowing and many babies are diagnosed with failure to thrive in the newborn period. This, however, usually lasts for about three to four months and then goes away. Hypotonia makes attaining fine motor skills (grasping, playing with toys, babbling) and gross motor skills (rolling, crawling, walking) difficult and these developmental milestones are usually delayed. Speech is also affected by hypotonia but as the child grows older and the hypotonia resolves or goes away, speech improves. Although the child may have delayed development, intellect typically is borderline to normal. Special attention may be needed in certain subjects, such as reading comprehension and arithmetic. Severe mental retardation is rarely seen.

There are a number of other features that have been associated with Sotos syndrome including jaundice in the newborn period, coordination problems, and a tendency for clumsiness. Behavioral problems and emotional immaturity are commonly reported. About half of the children with Sotos syndrome will experience a seizure associated with fever. Dental problems such as early eruption of teeth, excessive wear, discoloration, and gingivitis are common. Teeth may also be aligned incorrectly due to changes in the facial structure.

Infections tend to develop in the ear, upper respiratory tract and urinary tract. In some children, hearing may be disrupted due to recurrent ear infections and in these situations, a referral to an otolaryngologist (a doctor specializing in the ear, nose and throat) may be necessary for assessment of hearing. Urinary tract infections occur in about one out of five children with Sotos syndrome. These have been associated with structural problems of the bladder and ureters; consequently, if urinary tract infections occur, the child should undergo further evaluations.

Congenital heart problems and development of tumors have been reported in individuals with Sotos syndrome. However, as of 2001, the information regarding the actual risks of these problems is not definitive and medical screening for these conditions is not routinely recommended.

Genetic profile

Sotos syndrome is for the most part a sporadic condition, meaning that a child affected by it did not inherit it from a parent. In a very few families, autosomal dominant **inheritance** has been documented, which means that both a parent and his/her child is affected by Sotos syndrome. The cause of Sotos syndrome is not known and the gene(s) that are involved in it have not been identified.

Demographics

Sotos syndrome is described by different groups as being both “fairly common” and “rare”. A 1998 article in the *American Journal of Medical Genetics* states that over 300 cases of Sotos syndrome have been published and probably many more are unpublished. As of 2001, incidence numbers have not been determined. Sotos syndrome occurs in both males and females and has been reported in several races and countries.

Signs and symptoms

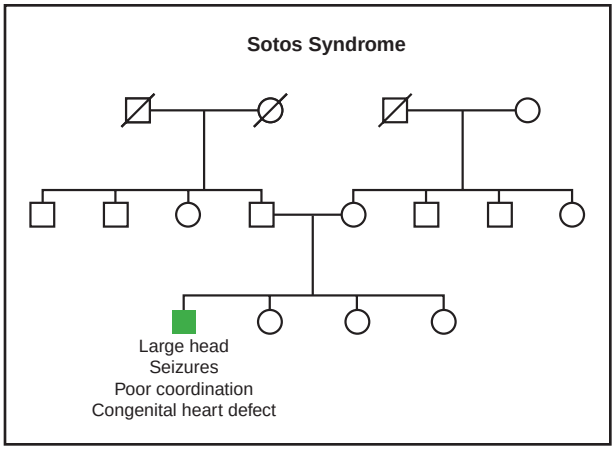
A variety of clincial features are associated with Sotos syndrome.

- Newborns are large with respect to length and head circumference; weight is usually average. The rapid growth continues through infancy and into childhood with the child's length/height and head circumference often being above the 97th percentile. The rate of growth appears to decrease in later childhood and adolescence.
- Respiratory and feeding problems (due to hyoptonia) may develop in the neonatal period.
- Infants have a round face with prominent forehead and small chin. As the child grows into adolescence and then adulthood the face becomes long and thin, and the chin becomes more prominent.
- Hypotonia is present at birth. This affects the development of fine and gross motor skills, and developmental milestones are usually delayed. Speech is also affected by hypotonia but as the child grows older and the hypotonia resolves or goes away, speech improves.
- Intellect typically is borderline to normal.
- Behavioral problems and emotional immaturity are commonly reported.
- Dental problems such as early eruption of teeth, excessive wear, discoloration, and gingivitis are common.

Diagnosis

Diagnosis of Sotos syndrome is based upon clinical examination, medical history and x ray data. There are no laboratory tests that can provide a diagnosis. The clinical criteria that are considered to be diagnostic for Sotos syndrome are excessive growth during the prenatal and postnatal period, advanced bone age, developmental delay, and a characteristic facial appearance. It should be noted that although features suggestive of Sotos syndrome may be present at birth or within 6-12 months after birth, making a diagnosis in infancy is not definitive and may take multiple evaluations over several years.

There are many conditions and genetic syndromes that cause excessive growth; consequently, a baby and/or child who has accelerated growth needs to be thoroughly examined by a physician knowledgeable in overgrowth and genetic syndromes. The evaluation includes asking about health problems in the family as well as asking about the growth patterns of the parents and their final height. In some families, growth patterns are different and thus may account for the child's excessive growth. The child will also undergo a complete physical examination. Additional examination of his/her facial appearance, with special attention paid to the shape of the head, width of the face at the level of the eyes, and appearance of the chin and forehead is necessary as well. Measurement of the head circumference, arm length, leg length, and wing span should be taken. Laboratory testing such as chromosome analysis (**karyotype**) may be done along with testing for another genetic syndrome called fragile-X. A bone age will also be ordered. Bone age is determined by x rays of the hand. If the child begins to lose developmental milestones or appears to stop developing, metabolic testing may be done to evaluate for a metabolic condition.



(Gale Group)

Treatment and management

There is no cure or method for preventing Sotos syndrome. However, the symptoms can be treated and managed. In the majority of cases, the symptoms developed by individuals with Sotos syndrome are treated and managed the same as in individuals in the general population. For example, physical and occupational therapy may help with muscle tone, speech therapy may improve speech, and behavioral assessments may assist with behavioral problems.

Managing the health of a child with Sotos syndrome includes regular measurements of the growth parameters, i.e. height, head circumference, and weight, although as of 2001, excessive growth is not treated. Regular eye and dental examinations are also recommended. As of 2001, medical screening for **congenital heart defects** and tumors is not routinely recommended, although it has been noted that symptoms should be evaluated sooner rather than later.

Prognosis

With appropriate treatment, management, and encouragement, children with Sotos syndrome can do well. Adults with Sotos syndrome are likely to be within the normal range for height and intellect. Sotos syndrome is not associated with a shortened life span.

Resources

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ORGANIZATIONS

Sotos Syndrome Support Group. Three Danda Square East #235, Wheaton, IL 60187. (888) 246-SSSA or (708) 682-8815. <http://www.well.com/user/sssa/>.

WEBSITES

Genetic and Rare Conditions Site. <http://www.kumc.edu/gec/support/>.

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Cindy L Hunter, CGC

Spastic cerebral palsy

Definition

Spastic **cerebral palsy** (CP) is a disorder in which brain damage results in a movement disability.

Description

Cerebral palsy is a nonprogressive disorder of movement and/or posture caused by a brain abnormality. It is evident before the age of two. There are several types of CP, but spastic CP is the most common—about 60%. The term "spasticity" refers to increased muscle tone (stiffness), leading to uncontrolled, awkward movements.

Genetic profile

Only about 2% of cases of CP are believed to result from genetic causes. Most cases of CP are associated with risk factors such as low birth weight, premature birth, and lack of oxygen at birth. Multiple births (such as twins or triplets) also have an increased risk. A genetic cause is more likely if these risk factors are not present. If the paralysis and spasticity are symmetrical—that is, if both sides of the body are similarly affected—then the condition is more likely to be genetic in nature. Mental retardation is usually, but not always, associated with genetic forms. Researchers have not yet found which **gene** is associated with the disease.

KEY TERMS

Cerebral palsy—Movement disability resulting from nonprogressive brain damage.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Demographics

CP has an overall incidence of one in 250 to 1,000 births. Most forms of CP that are genetic have an autosomal recessive pattern of **inheritance**. This means that in order for a child to have the disorder, they must inherit one altered copy of the causative gene from each parent. A person who has only one altered copy of the disease gene is called a carrier. Two carriers have a 25% chance of having a child with CP with each pregnancy. As studied in the British Pakistani population, a consanguineous marriage—marriage between relatives—appears to increase the prevalence of a genetic form of spastic CP.

Signs and symptoms

CP may not be noticed immediately after birth. Children with CP are slow to meet developmental motor milestones, which are expected ages at which certain mobility skills are achieved. These milestones include reaching for toys, sitting, and walking. People with CP also have abnormal muscle tone (increased in spastic CP), abnormal or uncontrolled movements, and abnormal reflexes. The spasticity may not be present at birth but usually develops during the first two years of life. Many children with spastic CP have normal intelligence, but mental retardation does occur, especially in inherited forms of the disease. Depending on the severity and extent of the paralysis, some affected individuals can walk (often late and with crutches or walkers), while others with more severe disability cannot walk at all. Seizures are not uncommon in individuals with CP.

Diagnosis

A diagnosis of spastic CP is based on delay in or lack of meeting developmental motor milestones, along with the presence of abnormal muscle tone, movements, and reflexes. Since the exact gene causing some cases of symmetric spastic CP has not yet been identified, molec-

ular testing is not available at this time. Since CP-like symptoms can be found in other genetic conditions, chromosome testing and molecular testing for other suspected conditions may help determine the cause of the CP-like symptoms. Testing may also enable other family members to be tested to see if they carry the condition, and to allow a fetus to be diagnosed prenatally. Prenatal diagnosis of known genetic conditions can be accomplished using procedures such as chorionic villi sampling, in which cells from the placenta are studied; and **amniocentesis**, in which skin cells from the fluid surrounding the fetus are studied.

Treatment and management

Treatment of spastic CP is focused on maximizing mobility through physical therapy, and/or providing necessary physical support using devices such as splints, walkers, and wheelchairs. Speech and occupational therapy are sometimes useful as well. Certain types of surgery of the bone, nerves, tendon, and brain tissue can correct abnormalities, improve mobility, and reduce spasticity. Orthodontic work on the teeth is often indicated in children with CP. Some level of special educational services is usually required.

Prognosis

Spastic CP is not a progressive condition, so living into old age is possible. However, complications such as reduced mobility, mental retardation, feeding difficulties, and respiratory infections can reduce the lifespan. More severe disabilities are associated with greater decreases in life expectancy, but at least half of people with CP live to at least age 35.

Resources

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United Cerebral Palsy Association, Inc. (UCP). 1660 L St. NW, Suite 700, Washington, DC 20036-5602. (202)776-0406 or (800)872-5827. <http://www.ucpa.org>.

Toni I. Pollin, MS, CGC

Spherocytosis, hereditary

Definition

Hereditary spherocytosis (HS) is a relatively common and highly variable inherited disorder of the red blood cells. In HS, red blood cells become sphere-shaped, instead of the usual biconcave (hourglass) shape. The hourglass shape is vital for the blood cells to function—it offers increased surface area so that oxygen and carbon dioxide can diffuse more easily through the cell's tissue, and the shape lets the cells circulate more easily in tight places, like small capillaries. These *spherocytes* are broken down more quickly than normal red blood cells, resulting in anemia and related complications.

Description

Hereditary spherocytosis results from a molecular change in one of the proteins making up the cytoskeleton of the red blood cell. The cytoskeleton consists of the network of proteins that support and maintain the integrity of the red cell membrane. Genetic mutations in membrane proteins lead to loss of these and related membrane components. As the membrane becomes unstable and the surface area of the membrane decreases, spherocytes form. The spleen provides an environment that encourages spherocyte formation. Due to their increased rigidity, spherocytes tend to become trapped in the spleen and then broken down by macrophages, specialized white blood cells. This hemolytic process most often leads to mild, chronic anemia. Depending in part on the particular genetic mutation underlying HS in a given individual, anemia can also be severe and require chronic blood transfusions. Additional complications related to anemia can arise.

Demographics

HS has been seen in individuals of many ethnic backgrounds, but is particularly common among people of northern European background, affecting about one in 5,000 of such individuals.

Genetic profile

About 75% of all cases of HS are due to the presence of an autosomal dominant mutation, one in which the mutated **gene** is passed on from either parent. Most of these cases result from the **inheritance** of a mutation from one parent, but a fourth of these cases are sporadic and due to a new mutation that has occurred in the affected individual. A minority of cases of HS is recessively inherited. HS-causing mutations have been described in four genes, each of which codes for a protein involved in maintaining stability of the red blood cell

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bilirubin—A yellow pigment that is the end result of hemoglobin breakdown. This pigment is metabolized in the liver and excreted from the body through the bile. Bloodstream levels are normally low; however, extensive red blood cell destruction leads to excessive bilirubin formation and jaundice.

Cytoskeleton—The network of proteins underlying and maintaining the integrity of the red blood cell membrane.

Encapsulated—Referring to bacteria that have a thick capsule protecting their cell wall.

Hemochromatosis—Accumulation of large amounts of iron in the tissues of the body.

Hemoglobin—Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hemolytic—Refers to the type of anemia caused by the breakdown of red blood cells, as opposed to anemia due to decreased production, for example.

Macrophage—Specialized white blood cells that play a role in breaking down old or abnormal red blood cells.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Red blood cell—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

Reticulocyte—Immature red blood cells.

Spherocytes—Red blood cells that are spherical in shape, as opposed to the normal bi-concave shape. Spherocytes are more rigid and their membranes are more fragile than normally-shaped red blood cells.

Spleen—Organ located in the upper abdominal cavity that filters out old red blood cells and helps fight bacterial infections. Responsible for breaking down spherocytes at a rapid rate.

membrane. The cytoskeleton can be thought of as a "scaffolding" or "frame" that is attached to and maintains the "wall" that is the cell membrane. The red cell membrane is made up of lipids, which are fat and fat-like molecules, and proteins called integral membrane proteins. The cytoskeleton lies just below the cell membrane and is made up of additional proteins, including spectrin, ankyrin, protein 4.1, and others.

Ankyrin

The ankyrin gene is located on the short arm of chromosome 8 (8p11.2). As of 1998, a total of 34 mutations in the ankyrin gene have been associated with HS. These account for 35–65% of all HS cases, including both dominant and recessive forms. Dominant-acting mutations tend to be those that result in a shortened ankyrin protein, including so-called frameshift and nonsense mutations. Recessive-acting mutations tend to be those that result in subtler changes to the protein. These include so-called missense mutations that result in the substitution of a single amino acid—the building block of proteins—which can have an effect on protein function. Recessive mutations also include those in the area "upstream" from the gene, in the promoter region that helps determine the quantity of protein made from the gene. Rarely, spherocytosis can be one symptom within a larger syndrome that is due to a deletion of a portion of chromosome 8. Such a microdeletion syndrome can affect several genes including the ankyrin gene, and there can be a range of physical and mental effects.

Spectrin

Spectrin is a cytoskeleton protein made of two components: alpha spectrin and beta spectrin. Two recessive mutations have been identified in the alpha spectrin gene on chromosome 1. This recessive form of the disease tends to have relatively severe hemolytic anemia. As of 1998, 19 mutations have been described in the beta spectrin gene on chromosome 14. These result in dominantly inherited HS.

Band 3 and others

Mutations in the gene for band 3, an integral membrane protein, account for 15–25% of all cases of HS. Five dominant mutations have been described, most of which result in a shortened protein. Disease-causing

mutations in other cytoskeleton or red cell membrane proteins are rare but have been described.

Modifying genetic factors

Disease severity is not only affected by the nature of the primary genetic mutation; it is also impacted by other genetic variations. Individuals with HS who also have Gilbert syndrome have an increased risk of gallstones. Gilbert syndrome is caused by a change in the UGT 1A1 gene that results in increased levels of bilirubin. Researchers have also hypothesized that persons with other inherited or acquired forms of hemolytic anemia may also be at increased risk of gallstones if they also have a disease-causing HS mutation. The presence of hereditary **hemochromatosis** in addition to HS increases the propensity toward iron-overload. Hereditary hemochromatosis is a relatively common recessive condition that can lead to organ failure due to iron-overload, if untreated.

Signs and symptoms

Symptoms of HS can be extremely variable. Some individuals may experience onset as early as the neonatal period and require treatment. Others may have only mild anemia that does not require treatment and does not become evident until later in life. Some individuals with few and subtle signs may even go undiagnosed. Variability is largely influenced by the primary underlying genetic mutation, with the recessive forms of the disease tending to be most severe. This does not account for all the variability, however, given that multiple affected individuals within the same family carrying the same genetic mutation may have symptoms of varying severity. The effects of modifying genes or environmental factors may contribute to this additional variability.

Anemia

The red blood cell membrane has increased fragility in HS. Therefore, red cells are more easily broken down, a symptom called hemolytic anemia. This occurs primarily in the spleen. The spleen filters out old and abnormal red blood cells, as well as fights infection from bacteria, particularly the encapsulated type. Anemia can be unnoticeable or mild, or it can be rapid and severe. Rapid, acute breakdown of red blood cells can occur as a result of exposure to chemicals or medications that are known to further increase red cell membrane fragility. It can also occur as a result of infection that increases the hemolytic activity of the spleen or decreases red blood cell production. Acute aplastic anemia events, in which red blood cell production halts, can occur with deficient folate levels or following infection by a specific virus called parvovirus.

Jaundice

Jaundice occurs when the level of bilirubin, a breakdown product of hemoglobin, increases. As red blood cells breakdown rapidly, the liver may not be able to keep up with the increased need to metabolize bilirubin, which can deposit in the skin and eyes causing a yellowish discoloration.

Gallstones

Bilirubin levels can also be increased in the bile. Bile is the fluid secreted by the liver into the intestine. Bile reaches the intestine by passing through the gallbladder and bile duct. Excess bilirubin can form stones in the gallbladder early in life.

Hemochromatosis

Hemochromatosis, or high iron levels, is also characteristic of HS. Iron-overload can lead to dysfunction of organ systems, including the endocrine system, which directs hormone levels.

Other complications

Leg ulcers are also seen in HS, and acute kidney failure due to hemolytic anemia is a rare complication. Rarely, HS can be seen within a syndrome as one symptom in combination with other complications such as neurological problems and other congenital physical differences. Such syndromes may be caused by the deletion of a portion of a chromosome including a gene known to be associated with HS, among other genes.

Diagnosis

HS must be distinguished from other causes of hemolytic anemia that can resemble HS. These include immune hemolytic anemia, G6PD deficiency, unstable hemoglobin traits or diseases, Wilson disease, and spherocytosis due to burn injury or toxin exposure (i.e. clostridia—bee, spider, or snake venom). Routine blood tests are typically sufficient to diagnose HS, particularly if an individual is showing symptoms. A peripheral blood smear, which is a slide preparation of a blood sample, will show the presence of a number of spherocytes that are uniform in appearance. Bilirubin levels tend to be elevated. A complete blood count will show several abnormalities. Hemoglobin levels tend to be decreased. Reticulocytes, which are immature red blood cells, tend to be increased. Red blood cells tend to be smaller than normal, which is marked by a decreased mean cell volume (MCV). The mean cell hemoglobin concentration (MCHC) tends to be high, which is a reflection of the overall decrease in the cell volume. Ektacytometry is a

specialized test that can demonstrate the fragility of the red blood cell membrane by placing the cells under stress and identifying increased levels and specific patterns of hemolysis. Another specialized test called the rapid flow cytometric test has recently been developed. This test can determine differences in fluorescent staining patterns that distinguish normal red blood cells from those that are characteristic of HS. This test is highly sensitive and specific for HS and should aid in its rapid diagnosis.

Treatment and management

Most individuals with HS do not have symptoms that are severe enough to require treatment. For those with the more severe forms, blood transfusion therapy can effectively improve symptoms until a child is old enough for total or partial removal of the spleen, the organ responsible for most of the red blood cell destruction. Splenectomy most often eliminates HS complications. However, there is some risk remaining for ongoing chronic anemia or acute anemic events, particularly those caused by viruses and other factors that can temporarily halt red blood cell production. Splenectomy can also lead to an increased risk for blood clots, as well as life-threatening bacterial infection given the spleen's role in fighting bacterial infections. Studies have shown that partial, as opposed to total, splenectomy can be effective at ameliorating HS symptoms while also maintaining the bacterial-fighting capacity of the spleen and decreasing the chance for blood clots. Prophylactic antibiotics (i.e. penicillin) and additional vaccinations for common bacterial infections also play a role in decreasing negative side-effects of partial or total splenectomy. Surgery may be needed to remove gallstones that become symptomatic, which usually does not occur until after age 10 years.

Prognosis

Prognosis is very good for all types of HS, particularly the more mild forms. Treatment is very effective for the more severe forms. There is only a small number of affected individuals who still experience anemia and other symptoms following splenectomy.

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Jennifer D. Bojanowski, MS, CGC

Sphingomyelin lipidosis *see* **Niemann-Pick disease**

Sphingomyelinease deficiency *see* **Niemann-Pick disease**

Spielmeyer-Vogt-Sjögren-Batten disease *see* **Batten disease**

Spina bifida

Definition

Spina bifida is a serious birth abnormality in which the spinal cord is malformed and lacks its usual protective skeletal and soft tissue coverings.

Description

Spina bifida may appear in the body midline anywhere from the neck to the buttocks. In its most severe form, termed spinal rachischisis, the entire spinal canal is open, exposing the spinal cord and nerves. More commonly, the abnormality appears as a localized mass on

the back that is covered by skin or by the meninges, the three-layered membrane that envelopes the spinal cord. Spina bifida is usually readily apparent at birth because of the malformation of the back and paralysis below the level of the abnormality.

Various forms of spina bifida are known as meningomyelocele, myelomeningocele, spina bifida aperta, open spina bifida, myelodysplasia, spinal dysraphism, spinal rachischisis, myelocele, and meningocele. The term meningocele is used when the spine malformation contains only the protective covering (meninges) of the spinal cord. The other terms indicate involvement of the spinal cord and nerves in the malformation. A related term, spina bifida occulta, indicates that one or more of the bony bodies in the spine are incompletely hardened, but that there is no abnormality of the spinal cord itself.

Genetic profile

Spina bifida may occur as an isolated abnormality or in the company of other malformations. As an isolated abnormality, spina bifida is caused by the combination of genetic factors and environmental influences that bring about malformation of the spine and spinal column. The specific genes and environmental influences that contribute to the many-factored causes of spina bifida are not completely known. An insufficiency of folic acid is known to be one influential nutritional factor. Changes (mutations) in genes involving the metabolism of folic acid are believed to be significant genetic risk factors. The recurrence risk after the birth of an infant with isolated spina bifida is 3-5%. Recurrence may be for spina bifida or another type of spinal abnormality.

Spina bifida may arise because of chromosome abnormalities, single gene mutations, or specific environmental insults such as maternal **diabetes mellitus** or prenatal exposure to certain anticonvulsant drugs. The recurrence risk varies with each of these specific causes.

Demographics

Spina bifida occurs worldwide, but there has been a steady downward trend in occurrence rates over the past 50-70 years, particularly in regions of high prevalence. The highest prevalence rates, about one in 200 pregnancies, have been reported from certain northern provinces in China. Intermediate prevalence rates, about one in 1,000 pregnancies, have been found in Central and South America. The lowest prevalence rates, less than one in 2,000 pregnancies, have been found in the European countries. The highest regional prevalence in the United States of about one in 500 pregnancies has occurred in the Southeast.

KEY TERMS

Chiari II anomaly—A structural abnormality of the lower portion of the brain (cerebellum and brain stem) associated with spina bifida. The lower structures of the brain are crowded and may be forced into the foramen magnum, the opening through which the brain and spinal cord are connected.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term embryo is used prior to the third month.

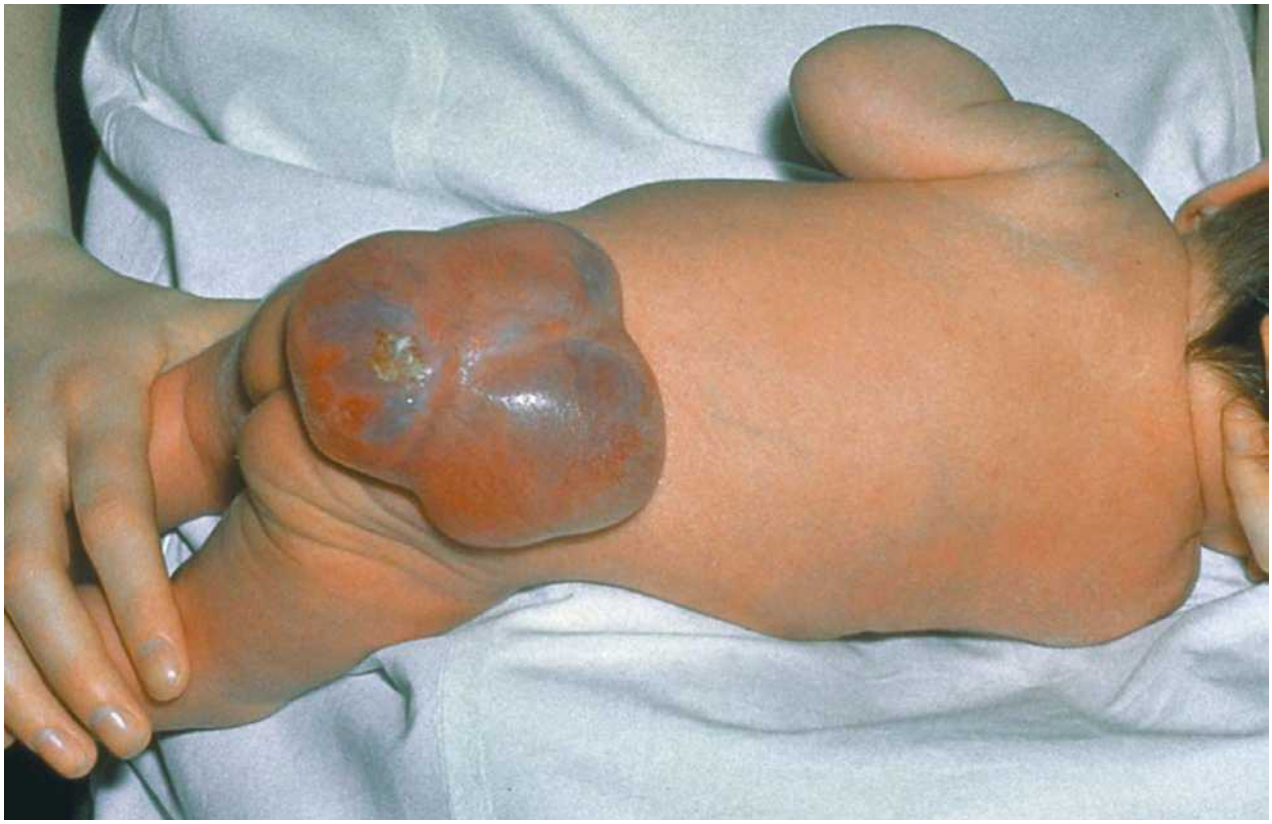
Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing

Signs and symptoms

In most cases, spina bifida is obvious at birth because of malformation of the spine. The spine may be completely open, exposing the spinal cord and nerves. More commonly, the spine abnormality appears as a mass on the back covered by membrane (meninges) or skin. Spina bifida may occur anywhere from the base of the skull to the buttocks. About 75% of abnormalities occur in the lower back (lumbar) region. In rare instances, the spinal cord malformation may occur internally, sometimes with a connection to the gastrointestinal tract.

In spina bifida, many complications arise, dependent in part on the level and severity of the spine malformation. As a rule, the nerves below the level of the abnormality develop in a faulty manner and fail to function, resulting in paralysis and loss of sensation below the level of the spine malformation. Since most abnormalities occur in the lumbar region, the lower limbs are paralyzed and lack sensation. Furthermore, the bowel and bladder have inadequate nerve connections, causing an inability to control bowel and bladder function. Most infants also develop hydrocephaly, an accumulation of excess fluid in the four cavities of the brain. At least one of every seven cases develop findings of Chiari II malformation, a condition in which the lower part of the brain is crowded and may be forced into the upper part of the spinal cavity.

There are a number of mild variant forms of spina bifida, including multiple vertebral abnormalities, skin dimples, tufts of hair, and localized areas of skin deficiency over the spine. Two variants, lipomeningocele and lipomyelomeningocele, typically occur in the lower back area (lumbar or sacral) of the spine. In these conditions,



An infant with spina bifida. The large fluid filled sac at the base of the spinal cord contains the meninges and possibly part of the spinal cord. *(Photo Researchers, Inc.)*

a tumor of fatty tissue becomes isolated among the nerves below the spinal cord, which may result in tethering of the spinal cord and complications similar to those with open spina bifida.

Diagnosis

Few disorders are to be confused with open spina bifida. The diagnosis is usually obvious based on the external findings at birth. Paralysis below the level of the abnormality and fluid on the brain (hydrocephaly) may contribute to the diagnosis. Other spine abnormalities such as congenital **scoliosis** and kyphosis, or soft tissue tumors overlying the spine, are not likely to have these accompanying findings. In cases in which there are no external findings, the diagnosis is more difficult and may not become evident until neurological abnormalities or hydrocephaly develop weeks, months, or years following birth.

Prenatal diagnosis may be made in most cases with ultrasound examination after 12-14 weeks of pregnancy. Many cases are also detected by the testing of the mother's blood for the level of alpha-fetoprotein at about 16 weeks of pregnancy. If the spine malformation is not skin covered, alpha-fetoprotein from the fetus' circulation may leak into the surrounding amniotic fluid, a small portion of which is absorbed into the mother's blood.

Treatment and management

Aggressive surgical and medical management have improved the survival and function of infants with spina bifida. Initial surgery may be carried out during the first days of life, providing protection against injury and infection. Subsequent surgery is often necessary to protect against excessive curvature of the spine, and in the presence of hydrocephaly, to place a mechanical shunt to decrease the pressure and amount of cerebrospinal fluid in the cavities of the brain. Because of weakness or paralysis below the level of the spine abnormality, most children will require physical therapy, bracing, and other orthopedic assistance to enable them to walk. A variety of approaches including periodic bladder catheterization, surgical diversion of urine, and antibiotics are used to protect urinary function.

Although most individuals with spina bifida have normal intellectual function, learning disabilities or mental impairment has occured. This may result, in part, from hydrocephaly and/or infections of the nervous system.

Children so affected may benefit from early educational intervention, physical therapy, and occupational therapy. Counseling to improve self-image and lessen barriers to socialization becomes important in late childhood and adolescence.

Open fetal surgery has been performed for spina bifida during the last half of pregnancy. After direct closure of the spine malformation, the fetus is returned to the womb. By preventing chronic intrauterine exposure to mechanical and chemical trauma, prenatal surgery improves neurological function and leads to fewer complications after birth. Fetal surgery is considered experimental, and results have been mixed.

Prevention of isolated spina bifida and other spinal abnormalities has become possible during recent decades. The major prevention is through the use of a B vitamin, folic acid, for several months prior to and following conception. The Centers for Disease Control and Prevention recommend the intake of 400 micrograms of synthetic folic acid every day for all women of childbearing years.

Prognosis

More than 80% of infants born with spina bifida survive with surgical and medical management. Although complications from paralysis, hydrocephaly, Chiari II malformation, and urinary tract deterioration threaten the well-being of the survivors, the outlook for normal intellectual function is good.

Resources

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ORGANIZATIONS

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Birth Defects Prevention Network. Atlanta, GA (770) 488-3550. <http://www.nbdpn.org>.

Shriners Hospitals for Children. International Shrine Headquarters, 2900 Rocky Point Dr., Tampa, FL 33607-1460. (813) 281-0300.

Spina Bifida Association of America. 4590 MacArthur Blvd. NW, Suite 250, Washington, DC 20007-4226. (800) 621-3141 or (202) 944-3285. Fax: (202) 944-3295.

WEBSITES

Spina Bifida Association of America. <http://www.sbaa.org>.

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Roger E. Stevenson, MD

Spinal and bulbar muscular atrophy *see* **Kennedy disease**

Spinal muscular atrophy

Definition

Spinal muscular atrophy (SMA) is a disease characterized by degradation of the anterior horn cells of the spinal cord and has similar characteristics to Spinobulbar muscular atrophy (SBMA). SBMA differs from SMA in its mode of **inheritance**, the disease-determining **gene**, the mutational events that trigger disease and the cellular specificity of the disease pathology.

Description

The anterior horn cells control the voluntary muscle contractions from large muscle groups such as the arms and legs. For example, if an individual wants to move his/her arm, electrical impulses are sent from the brain down the anterior horn cells to the muscles of the arm, which then stimulates the arm muscles to contract allowing the arm to move. Degradation is a rapid loss of functional motor neurons. Loss of motor neurons results in progressive symmetrical atrophy of the voluntary muscles. Progressive symmetrical atrophy refers to the loss of function of muscle groups from both sides of the body. For example, both arms and both legs are equally effected to similar degrees of muscle loss and the inability to be controlled and used properly. Progressive loss indicates that muscle loss is not instantaneous, rather, muscle loss occurs consistantly over a period of time. These muscle groups include those skeletal muscles that control large muscle groups such as the arms, legs and torso. The weakness in the legs is generally greater than the weakness in the arms.

Spinal muscular atrophy (SMA) arises primarily from degradation of the anterior horn cells of the spinal cord, resulting in proximal weakness and atrophy of voluntary skeletal muscle. Proximal weakness effects the limbs positioned closer to the body, such as arms and legs, rather than more distant body parts such as hands, feet, fingers, or toes.

Spinal muscular atrophy only affects the motor neurons of the spinal cord and voluntary muscles of the limb

KEY TERMS

Anterior horn cells—Subset of motor neurons within the spinal cord.

Atrophy—Wasting away of normal tissue or an organ due to degeneration of the cells.

Degradation—Loss or diminishing.

Dorsal root ganglia—The subset of neuronal cells controlling impulses in and out of the brain.

Intragenic—Occuring within a single gene.

Motor neurons—Class of neurons that specifically control and stimulate voluntary muscles.

Motor units—Functional connection with a single motor neuron and muscle.

Sensory neurons—Class of neurons that specifically regulate and control external stimuli (senses: sight, sound).

Transcription—The process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

Voluntary muscle—A muscle under conscious control, such as arm and leg muscles.

and trunk. Patients do not display sensory loss, heart problems, or mental retardation. There are numerous secondary complications seen in SMA, including bending of the legs and arms and pneumonia. SMA development involves an initial substantial loss of motor units, followed by a stabilization of the surviving motor units. Motor units refer to an entire motor neuron and the connections within a muscle required for neuronal function.

Clinical subgroups

The childhood form of SMA is subdivided into three main clinical subgroups, Type I, II, and III, depending upon the age of onset and severity. A fourth subgroup, Type O, was recently discovered in London.

Type I

Type I SMA, or Werdnig-Hoffmann disease, is the acute or severe form, characterized by severe muscle atrophy. Guido-Werdig, an Austrian doctor, first identified the disease in 1891. He described two brothers displaying progressive muscle weakness from the age of 10 months, starting in the legs and progressing to the back and arms. The first brother died at the age three years with respiratory problems. The second brother survived to the age of six years.

Symptoms emerge in the first three months of life with the affected children never gaining the ability to sit, stand, or walk. Swallowing and feeding may be difficult and the child may show difficulties with their own secretions. There is general weakness in the intercostals and accessory respiratory muscles (the muscles situated between the ribs). The chest may appear concave (sunken in) due to the diaphragmatic (tummy) breathing.

Type II

Type II SMA was first described in 1964. It is less severe than type I, with clinical symptoms emerging between three and 15 months of age. Most patients can sit but are unable to stand or walk unaided. Feeding and swallowing problems are uncommon in patients with Type II SMA. Again, as with patients diagnosed with type I SMA, the intercostal muscles are affected, with diaphragmatic breathing a main characteristic of children with type II. Most patients will survive beyond the age of four years and, depending upon how their respiratory system is affected, may live through adolescence.

Type III

The chronic form of SMA, Type III (Kugelberg-Welander disease) was first described in 1956. The clinical symptoms manifest after the age of four. It produces proximal muscle weakness, predominantly in the lower body. Affected individuals can walk unaided and have a normal life span depending upon the extent of respiratory muscles loss.

Type O

Clinicians in London have recently identified a fourth form of the childhood disease; Type 0 SMA. This form appears to have a fetal-onset in that affected individuals display reduced movement within the uterus and are born with severe muscular atrophy with massive motor neuronal cell death. Therefore, these patients have very few functional motor neurons and motor units.

Diagnosis

One of the main diagnostic tools is electromyography (EMG). Contraction of voluntary muscle is controlled by electrical impulses originating from the brain. These impulses pass down the motor neurons of the spinal cord to the connecting muscles, where it triggers the contraction. The EMG records this electrical impulse and determines whether the electric current is the same as in normal individuals. Metal needles are inserted into the arms and thigh and the electrical impulse is recorded.

In addition, the speed at which the electric impulse passes down the motor neuron can also be used as a diag-

nostic test. In SMA patients, both the nerve conduction velocity (NVC) and the EMG readings are reduced.

The third test is an invasive procedure called a muscle biopsy. This involves a surgeon removing a small section of muscle. This is then tested for signs of degradation.

Genetic profile

All forms of childhood SMA are autosomal recessive, with both parents needing to be carriers to pass the disease on. If both parents are carriers, there is a 25% chance of their child being affected.

All three forms are caused by a decrease in the production of a protein, termed Survival of Motor Neuron (SMN). The SMN protein is encoded by two nearly identical genes located on chromosome 5; SMN-1 and SMN-2 (previously referred to as telomeric and centomeric SMN, respectively). Remarkably, only mutations or deletions of SMN-1 result in disease development.

In most individuals who do not have SMA, each chromosome (maternal and paternal) contains one copy of SMN-1 and one copy of SMN-2. Therefore, in most unaffected individuals, there are two SMN-1 and two SMN-2 genes. Importantly, a subset of SMA-causing mutations are intragenic SMN-1 single amino acid substitutions. Intragenic indicates that mutations are within an otherwise intact SMN gene, but that there is a small and very subtle mutation that is only found within the SMN gene. This is in contrast to large genomic deletions that can delete the SMN gene and also neighboring genes. The intragenic or small mutations thereby confirms SMN-1 as the SMA-determining gene.

Signs and symptoms

Research shows that, in SMA, the reduced SMN protein levels result in motor neuronal cell degradation. How, and why this occurs is still not known.

Demographics

Approximately, one in 10,000 live births are affected with SMA, which is slightly lower than expected since the carrier frequency is between one in 40 and one in 50. Since this is a recessive disease, meaning two copies of the abnormal gene must be present for the disease to occur, carriers are unaffected because only one copy of the abnormal gene is present.

The genomic SMN region is remarkably unstable, and *de novo* mutations (mutations that are new and not inherited from the parents) are quite frequent, accounting for nearly 2% of all SMA cases. In 90% of patients, death occurs before the age of two due to respiratory failure. In North America and Europe, type I SMA accounts for one in every 25,000 infant mortalities. SMA is the leading genetic cause of infantile death and is the second most common autosomal recessive disorder behind **cystic fibrosis**. Carrier frequencies and disease frequencies are similar throughout the world, although slight variations can exist. Asian populations have a slightly reduced carrier frequency although it is not known why this discrepancy has occurred.

Treatment and management

To date, there is no treatment for childhood SMA. However, there are possible mechanisms through which treatment could be developed. **Gene therapy** could be used for SMA to replace the abnormal SMN-1 gene. Such treatment is not yet available or possible at this time though.

Prognosis

In Type I SMA, eating and swallowing can become difficult as the muscles of the face are affected. Due to the degradation of the respiratory muscles breathing can also be labored. It is therefore essential for patients to undergo chest physiotherapy (CPT). CPT is a standard set of procedures designed to trigger and aid coughing in patients. Coughing is important as it clears the patients lungs and throat of moisture and prevents secondary problems, such as pneumonia.

As symptoms progress, patients may require a ventilator to aid breathing. There are two main forms of ventilation systems. Negative Pressure Ventilation can be achieved by placing the patient in a Port-A-Lung. This machine ensures that the air pressure around the patient is lower than the air pressure within the patient's lungs, enabling easier breathing. The pressure can be raised or lowered if the patients ventilation rate increases or decreases.

The second method is called Bi-Pap (Biphasic Positive Airway Pressure). This procedure involves the insertion of a small tube down the nose into the patient's lungs, through which oxygen is pumped into the lungs and waste carbon dioxide is removed. This system allows maximum inspiration and expiration levels to be reached.

Of all the forms of childhood SMA, Type II is the most diverse. It is therefore hard to tell when muscle weakness will occur and how severe the disease will be. With the aid of leg braces and walking devices, some children may gain the ability to stand. Unlike Type I SMA, not all children with Type II are affected by respiratory weakness. The main cause of death in patients with Type II is respiratory failure resulting from a

respiratory infection. It is therefore important to ensure that mucus does not build up in patients respiratory tracts as this could aid viral and bacterial infections.

Resources

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ORGANIZATIONS

Muscular Dystrophy Association. 3300 East Sunrise Dr., Tucson, AZ 85718. (520) 529-2000 or (800) 572-1717. <http://www.mdausa.org>.

WEBSITES

Families of Spinal Muscular Atrophy. <http://www.fsma.org>.
The Andrew's Buddies web site. *FightSMA.com* <http://www.andrewsbuddies.com/news.html>.

Philip J. Young
Christian L. Lorson, PhD

Spinocerebellar ataxia

Definition

The spinocerebellar ataxias (SCAs) are a group of inherited conditions that affect the brain and spinal cord causing progressive difficulty with coordination.

Description

The SCAs are named for the parts of the nervous system that are affected in this condition. *Spino* refers to the spinal cord and *cerebellar* refers to the cerebellum or back part of the brain. The cerebellum is the area of the brain that controls coordination. In people with SCA, the cerebellum often becomes atrophied or smaller. Symptoms of SCA usually begin in the 30s or 40s, but onset can be at any age. Onset from childhood through the 70s has been reported.

As of early 2001, at least 13 different types of SCA have been described. This group is numbered 1-14 and each is caused by mutations or changes in a different **gene**. Although the category of SCA9 has been reserved, there is no described condition for SCA9 and no gene has been found. Spinocerebellar ataxia has also been called olivopontocerebellar atrophy, Marie's ataxia, and cerebellar degeneration. SCA3 is sometimes called Machado-Joseph disease named after two of the first families described with this condition. All affected people in a family have the same type of SCA.

Genetic profile

Although each of the SCAs is caused by mutations in different genes, the types of mutations are the same in all of the genes that have been found. Most genes come in pairs; one member of a pair comes from a person's mother and the other one comes from their father. The genes are made up of deoxyribonucleic acid (**DNA**) and the DNA is made up of chemical bases that are represented by the letters C, T, G, and A. This is the DNA alphabet. The letters are put together in three letter words. The arrangement of the words are what give the gene its meaning and therefore tells the body how to grow and develop.

Trinucleotide repeats

In each of the genes that cause SCA, there is a section of the gene where a three letter word is repeated a certain number of times. In most of the types of SCA, the word that is repeated is CAG. So there is a part of the gene that reads CAGCAGCAGCAGCAG...and so on. In people who have SCA, this word is repeated too many times. Therefore, this section of the gene is too big. This is called a trinucleotide repeat expansion. In SCA8 the word that is repeated is CTG. In SCA10, the repeated word is five DNA letters long and is ATTCT. This is called a pentanucleotide expansion. The actual number of words that is normal or that causes SCA is different in each type of SCA.

In each type of SCA, there are a certain number of words that are normal (the normal range). People who have repeat numbers in the normal range will not develop SCA and cannot pass it to their children. There is also a certain number of repeats that cause SCA (the affected range). People who have repeat numbers in the affected range will go on to develop SCA sometime in their lifetime if they live long enough. People with repeat numbers in the affected range can pass SCA onto their children. Between the normal and affected ranges there is a gray range. People who have repeat numbers in the gray range may or may not develop SCA in their lifetime. Why some people with numbers in the gray zone develop SCA and others do not is not known. People with repeat numbers in the gray range can also pass SCA onto their children.

In general, the more repeats in the affected range that someone has, the earlier the age of onset of symptoms and the more severe the symptoms. However, this is a general rule. It is not possible to look at a person's repeat number and predict at what age they will begin to have symptoms or how their condition will progress.

Anticipation

Sometimes when a person who has repeat numbers in the affected or gray range has children, the expansion

grows larger. This is called anticipation. This can result in an earlier age of onset in children than in their affected parent. Anticipation does not occur in SCA6. Significant anticipation can occur with SCA7. It is not unusual for a child with SCA7 to be affected before their parent or even grandparent begins to show symptoms. In most types of SCA, anticipation happens more often when a father passes SCA onto his children then when a mother passes it. However, in SCA8 the opposite is true; anticipation happens more often when a mother passes it to her children. Occasionally, repeat sizes stay the same or even get smaller when they are passed to a person's children.

Inheritance

The SCAs are passed on by autosomal dominant **inheritance**. This means that males and females are equally likely to be affected. It also means that only one gene in the pair needs to have the mutation in order for a person to become affected. Since a person only passes one copy of each gene onto their children, there is a 50% or one in two chance that a person who has SCA will pass it on to each of their children. A person who has repeat numbers in the gray range also has a 50% or one in two chance of passing the gene on to each of their children. However, whether or not their children will develop SCA depends on the number of their repeats. A person who has repeat numbers in the normal range cannot pass SCA onto their children.

New mutations

Usually a person with SCA has a long family history of the condition. However, sometimes a person with SCA appears to be the only one affected in the family. This can be due to a couple of reasons. First, it is possible that one of their parents is or was affected, but died before they began to show symptoms. It is also possible that their parent had a mutation in the gray range and was not affected, but the mutation expanded into the affected range when it was passed on. Other family members may also have SCA but have been misdiagnosed with another condition or are having symptoms, but have no diagnosis. It is also possible that a person has a new mutation for SCA. New mutations are changes in the gene that happen for the first time in an affected person. Although a person with a new mutation may not have other affected family members, they still have a 50% or one in two chance of passing it on to their children.

Demographics

SCA has been found in people from all over the world. However, some of the types of SCA may be more common in certain areas and ethnic groups. SCA types 1, 2, 3, 6, and 7 account for the majority of autosomal dominant SCA. SCA3 appears to be the most common type and was first described in families from Portugal. SCA3 also seems to be the most common type in Germany. SCA8 accounts for about 2-5% of all SCA. SCA types 4, 5, 10, 11, 12, 13, and 14 are rare and have each only been described in a few families. The first family described with SCA5 may have been distantly related to President Abraham Lincoln and was first called Lincoln ataxia. As of early 2001, SCA10 has only been described in Mexican families, SCA13 has only been described in one French family, and SCA14 has only been found in one family from Japan.

KEY TERMS

Anticipation—Increasing severity in disease with earlier ages of onset, in successive generations; a condition that begins at a younger age and is more severe with each generation

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Trinucleotide repeat expansion—A sequence of three nucleotides that is repeated too many times in a section of a gene.

Signs and symptoms

Although different genes cause each of the SCAs, they all have similar symptoms. All people with SCA have ataxia or a lack of muscle coordination. Walking is affected and eventually the coordination of the arms, hands, and of the speech and swallowing is also affected. One of first symptoms of SCA is often problems with walking and difficulties with balance. The muscles that control speech and swallowing usually become affected. This results in dysarthria or slurred speech and difficulties with eating. Choking while eating can become a significant problem and can lead to a decrease in the number of calories a person can take in. The age of the onset of symptoms can vary greatly—anywhere from childhood through the seventh decade have been reported. The age of onset and severity of symptoms can also vary between people in the same family.

As the condition progresses, walking becomes more difficult and it is necessary to use a cane, walker, and eventually a wheelchair. Because of the uncoordinated walking that develops, it is not uncommon for people with SCA to be mistaken for being intoxicated. Carrying

around a note from their doctor explaining their medical condition can often be helpful.

Some of the SCA types can also have other symptoms, although not all of these are seen in every person with that particular type. SCA2: People with this type may have slower eye movements. This does not usually interfere with a person's sight. SCA3: In this type people may develop problems with the peripheral nerves—those nerves that carry information to and from the spinal cord. This can lead to decreased sensation and weakness in the hands and feet. In SCA3 people may also have twitching in the face and tongue, and bulging eyes. SCA4: People with this type may have a loss of sensation but often have a normal lifespan. SCA5: This type often has an adult onset and is slowly progressive, not affecting a person's lifespan. SCA6: This type often has a later onset, progresses very slowly and does not shorten a person's life. SCA7: Progressive visual loss that eventually leads to blindness always happens with this type. SCA10: A few people with this type have had seizures. SCA11: This type is relatively mild and people have a normal lifespan. SCA12: People often have a tremor as the first noticeable symptom and may eventually develop **dementia**. SCA13: Some people with this type are shorter than average and have mild mental retardation.

Diagnosis

An initial workup of people who are having symptoms of ataxia will include questions about a person's medical history and a physical examination. Blood work to rule out other causes of the ataxia such as vitamin deficiencies may also be done. Magnetic resonance imaging (MRI) of the brain in people with SCA will usually show degeneration or atrophy of the cerebellum and may be helpful in suggesting a diagnosis of SCA. A thorough family history should be taken to determine if others in the family have similar symptoms and the inheritance pattern in the family.

Since there is so much overlap between symptoms in the different types of SCA, it is not usually possible to tell the different types apart based on clinical symptoms. The only way to definitively diagnose SCA and determine a specific subtype is by **genetic testing**. This involves drawing a small amount of blood. The DNA in the blood cells is then examined and the number of CAG repeats in each of the SCA genes are counted. As of early 2001, clinical testing is available to detect the mutations that cause SCA1, 2, 3, 6, 7, 8, and 10.

If genetic testing is negative for the available testing, it does not mean that a person does not have SCA. It could mean that they have a type of SCA for which genetic testing is not yet available.

Predictive testing

It is possible to test someone who is at risk for developing SCA before they are showing symptoms to see whether they inherited an expanded trinucleotide repeat. This is called predictive testing. Predictive testing cannot determine the age of onset that someone will begin to have symptoms, or the course of the disease. The decision to undergo this testing is a very personal decision and one that a person can only make for his or her self. Some people choose to have testing so that they can make decisions about having children or about their future education, career, or finances. Protocols for predictive testing have been developed, and only certain centers perform this testing. Most centers require that the diagnosis of SCA has been confirmed by genetic testing in another family member. It is also strongly suggested that a person have a support person, either a spouse or close friend, be with them at all visits.

A person who is interested in testing will be seen by a team of specialists over the course of a few visits. Often they will meet a neurologist who will perform a neurological examination to see if they may be showing early signs of the condition. If a person is having symptoms, testing may be performed to confirm the diagnosis. The person will also meet with a genetic counselor to talk about SCA, how it is inherited, and what testing can and cannot tell someone. They will also explore reasons for testing and what impact the results may have on their life, their family, their job and their insurance. Most centers also require a person going through predictive testing to meet a few times with a psychologist. The purpose of this visit is to make sure that the person has thought through the decision to be tested and is prepared to deal with whatever the results may be. These visits also allow a person to make contact with someone who can help him or her deal with the results if necessary. All centers require that results are given in person and usually require that a person come in for a few follow-up visits, regardless of the testing results.

These protocols are not in place to make people go through endless steps to get testing. Rather they have been developed to make sure that people make the best decision for themselves, their life, and their family and that they are prepared to cope with the results, whatever the outcome. Once the results are given, it is not possible to give them back or forget them. People should therefore take the testing process seriously and give a great deal of consideration to making the decision to be tested.

Testing children

If a child is having symptoms, it is appropriate to perform testing to confirm the cause of their symptoms.

However, testing will not be performed on children who are at risk for developing SCA but are not having symptoms. The choice to know this information can only be made for oneself when they are old enough to make a mature decision. Testing a child who does not have symptoms could lead to possible problems with their future relationships, education, career, and insurance.

Prenatal testing

Testing a pregnancy to determine whether an unborn child is affected is possible if genetic testing in a family has identified a certain type of SCA. This can be done at 10-12 weeks gestation by a procedure called chorionic villus sampling (CVS) that involves removing a tiny piece of the placenta and examining the cells. It can also be done by **amniocentesis** after 16 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it and those who are interested in learning more should check with their doctor or genetic counselor. Continuing a pregnancy that is found to be affected is like performing predictive testing on a child. Therefore couples interested in these options should have **genetic counseling** to carefully explore all of the benefits and limitations of these procedures.

There is also another procedure, called preimplantation diagnosis that allows a couple to have a child that is unaffected with the genetic condition in their family. This procedure is experimental and not widely available. Those interested in learning more about this procedure should check with their doctor or genetic counselor.

Treatment and management

Although there is a lot of ongoing research to try to learn more about SCA and develop treatments, no cure currently exists for the SCAs. Although vitamin supplements are not a cure or treatment for SCA, they may be recommended if a person is taking in fewer calories because of feeding difficulties. Different types of therapy might be useful to help people maintain as independent a lifestyle as possible. An occupational therapist may be able to suggest adaptive devices to make the activities of daily living easier. For example they may suggest installing bars to use in the bathroom or shower or special utensils for eating. A speech therapist might be able to make recommendations for devices that might make communication easier as the speech becomes affected. As swallowing becomes more difficult, a special swallow evaluation may lead to better strategies for eating and to lessen the risk of choking.

Genetic counseling

Genetic counseling helps people and their families to make decisions about their medical care, genetic testing, and having children by providing information and support. It can also help people to deal with the medical and emotional issues that arise when there is a genetic condition diagnosed in the family.

Prognosis

Most people with the SCAs do have progression of their symptoms that leads to full time use of a wheelchair. The duration of the disease after the onset of symptoms is about 10-30 years, but can vary depending in part to the number of trinucleotide repeats and age of onset. In general, people with a larger number of repeats have an earlier age of onset and more severe symptoms. Choking can be a major hazard because if food gets into the lungs, a life-threatening pneumonia can result. As the condition progresses, it can become difficult for people to cough and clear secretions. Most people die from respiratory failure or pulmonary complications.

Resources

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Zohgbi, H.Y., and H.T. Orr. “Glutamine Repeats and Neurodegeneration.” *Mayo Clinic Proceedings* (2000): 217-247.

ORGANIZATIONS

National Ataxia Foundation. 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447. (763) 553-0020. Fax: (763) 553-0167. naf@ataxia.org. <http://www.ataxia.org>.

WE MOVE (Worldwide Education and Awareness for Movement Disorders) 204 E. 84th St., New York, NY 10024. (212) 875-8312 or (800) 437-MOV2. Fax: (212) 875-8389. wemove@wemove.org. <http://www.wemove.org>.

WEBSITES

GeneClinics. <http://www.geneclinics.org>.

Online Mendelian Inheritance in Man. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>.

International Network of Ataxia Friends (INTERNAF). <http://www.internaf.org>.

Spinocerebellar Ataxia: Making an Informed Choice about Genetic Testing. <http://www.depts.washington.edu/neurogen/AtaxiaBrochure99.pdf>.

Karen M. Krajewski, MS

Spinocerebellar atrophy I *see* Spinocerebellar ataxia

Spondyloepiphyseal dysplasia

Definition

Spondyloepiphyseal **dysplasia** is a rare hereditary disorder characterized by growth deficiency, spinal malformations, and, in some cases, ocular abnormalities.

Description

Spondyloepiphyseal dysplasia is one of the most common causes of short stature. There are two forms of spondyloepiphyseal dysplasia. Both forms are inherited and both forms are rare.

Congenital spondyloepiphyseal dysplasia

Congenital spondyloepiphyseal dysplasia is primarily characterized by prenatal growth deficiency and spinal malformations. Growth deficiency results in short stature (dwarfism). Abnormalities of the eyes may be present, including nearsightedness (**myopia**) and retina (the nerve-rich membrane lining the eye) detachment in approximately half of individuals with the disorder. Congenital spondyloepiphyseal dysplasia is inherited as an autosomal dominant genetic trait.

Congenital spondyloepiphyseal dysplasia is also known as SED, congenital type; SED congenita; and SEDC.

Spondyloepiphyseal dysplasia tarda

Spondyloepiphyseal dysplasia tarda primarily affects males. It is characterized by dwarfism and hunched appearance of the spine. The disorder doesn't become evident until five to 10 years of age. Spondyloepiphyseal dysplasia tarda is an X-linked recessive inherited disorder.

Spondyloepiphyseal dysplasia tarda is also known as SEDT; spondyloepiphyseal dysplasia, late; and SED tarda, X-linked.

Genetic profile

Both forms of the disorder are inherited, however they are inherited differently.

Congenital spondyloepiphyseal dysplasia

Congenital spondyloepiphyseal dysplasia is thought to probably always result from abnormalities in the COL2A1 **gene**, which codes for type II collagen. Collagen is a protein that is a component of bone, cartilage, and connective tissue. A variety of abnormalities (such as deletions and duplications) involving the COL2A1 gene may lead to the development of the disorder.

It is one of a group of skeletal dysplasias (dwarfing conditions) caused by changes in type II collagen. These include hypochondrogenesis; spondyloepimetaphyseal dysplasia, Strudwick (SEMD); and Kniest dysplasia. Type 2 collagen is the major collagen of a component of the spine called the nucleus pulposa, of cartilage, and of vitreous (a component of the eye). All of these conditions have common clinical and radiographic findings including spinal changes resulting in dwarfism, myopia, and retinal degeneration.

Congenital spondyloepiphyseal dysplasia is inherited as an autosomal dominant genetic trait. In autosomal dominant **inheritance**, a single abnormal gene on one of the autosomal **chromosomes** (one of the first 22 "non-sex" chromosomes) from either parent can cause the disease. One of the parents will have the disease (since it is dominant) and is the carrier. Only one parent needs to be a carrier in order for the child to inherit the disease. A child who has one parent with the disease has a 50% chance of also having the disease.

Autosomal recessive inheritance of congenital spondyloepiphyseal dysplasia has been considered in cases when a child with the disorder is born to parents who are not affected by the disorder. It considered more likely that in these cases the disorder resulted from germline mosaicism in the collagen Type II gene of the parent. Germline mosaicism occurs when the causal mutation, instead of involving a single germ cell, is carried only by a certain proportion of the germ cells of a given parent. Thus, the parent carries the mutation in his or her germ cells and therefore runs the risk of generating more than one affected child, but does not actually express the disease.

Spondyloepiphyseal dysplasia tarda

Spondyloepiphyseal dysplasia tarda is caused by mutations in the SEDL gene, which is located on the X chromosome at locus Xp22.2-p22.1.

Spondyloepiphyseal dysplasia tarda is inherited as an X-linked disorder. The following concepts are important to understanding the inheritance of an X-linked disorder. All humans have two chromosomes that determine their gender: females have XX, males have XY. X-linked recessive, also called sex-linked, inheritance affects the genes located on the X chromosome. It occurs when an unaffected mother carries a disease-causing gene on at least one of her X chromosomes. Because females have two X chromosomes, they are usually unaffected carriers. The X chromosome that does not have the disease-causing gene compensates for the X chromosome that does. For a woman to show symptoms of the disorder, both X chromosomes would have the disease-causing gene. That is why women are less likely to show such symptoms than males.

If a mother has a female child, the child has a 50% chance of inheriting the disease gene and being a carrier who can pass the disease gene on to her sons. On the other hand, if a mother has a male child, he has a 50% chance of inheriting the disease-causing gene because he has only one X chromosome. If a male inherits an X-linked recessive disorder, he is affected. All of his daughters will be carriers, but none of his sons.

Demographics

It has been estimated that spondyloepiphyseal dysplasia affects about one in 100,000 individuals.

Congenital spondyloepiphyseal dysplasia affects both males and females. Spondyloepiphyseal dysplasia tarda affects mostly males.

Signs and symptoms

Congenital spondyloepiphyseal dysplasia

Congenital spondyloepiphyseal dysplasia is characterized by these main features:

- Prenatal growth deficiency occurs prior to birth, and growth deficiencies continue after birth and throughout childhood, resulting in short stature (dwarfism). Adult height ranges from approximately 36-67 in (91-170 cm).
- Spinal malformations include a disproportionately short neck and trunk and a hip deformity wherein the thigh bone is angled toward the center of the body (coxa vara). Abnormal front-to-back and side-to-side curvature of the spine (kyphoscoliosis) may occur, as may an abnormal inward curvature of the spine (lumbar lordosis). Spinal malformations are partially responsible for short stature.
- Hypotonia (diminished muscle tone), muscle weakness, and/or stiffness is exhibited in most cases.
- Progressive nearsightedness (myopia) may develop and/or retina detachment. Retinal detachment, which can result in blindness, occurs in approximately 50% of cases.
- An abnormally flat face, underdevelopment of the cheek bone (malar hypoplasia), and/or cleft palate may present in some individuals with congenital spondyloepiphyseal dysplasia.
- Additional associated abnormalities may include underdevelopment of the abdominal muscles; a rounded, bulging chest (barrel chest) with a prominent sternum (pectus carinatum); diminished joint movements in the lower extremities; the heel of the foot may be turned inward toward body while the rest of the foot is bent downward and inward (**clubfoot**); and rarely, hearing impairment due to abnormalities of the inner ear may occur.

The hypotonia, muscle weakness, and spinal malformations may result in a delay in affected children learning to walk. In some cases, affected children may exhibit an unusual "waddling" gait.

Spondyloepiphyseal dysplasia tarda

Symptoms of spondyloepiphyseal dysplasia tarda are not usually apparent until 5-10 years of age. At that point, a number of symptoms begin to appear:

- Abnormal growth causes mild dwarfism.
- Spinal growth appears to stop and the trunk is short.
- The shoulder may assume a hunched appearance.
- The neck appears to become shorter.
- The chest broadens (barrel chest).
- Additional associated abnormalities may include unusual facial features such as a flat appearance to the

KEY TERMS

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Coxa vara—A deformed hip joint in which the neck of the femur is bent downward.

Dysplasia—The abnormal growth or development of a tissue or organ.

Hypotonia—Reduced or diminished muscle tone.

Kyphoscoliosis—Abnormal front-to-back and side-to-side curvature of the spine.

Lumbar lordosis—Abnormal inward curvature of the spine.

Malar hypoplasia—Small or underdeveloped cheekbones.

Myopia—Nearsightedness. Difficulty seeing objects that are far away.

Ochronosis—A condition marked by pigment deposits in cartilage, ligaments, and tendons.

Ossification—The process of the formation of bone from its precursor, a cartilage matrix.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

face. Progressive degenerative arthritis may affect hips and other joints of the body.

Spine and hip changes become evident between 10 and 14 years of age. In adolescence, various skeletal abnormalities may cause pain in the back, hips, shoulders, knees, and ankles, a large chest cage and relatively normal limb length. In adulthood, height usually ranges from 52 to 62 inches; hands, head and feet appear to be normal size.

Diagnosis

X rays may be used to diagnose spondyloepiphyseal dysplasia when it is suspected.

Congenital spondyloepiphyseal dysplasia

Individuals with congenital spondyloepiphyseal dysplasia have characteristic x rays that show delayed ossification of the axial skeleton with ovoid vertebral bodies. With time, the vertebral bodies appear flattened. There is delayed ossification of the femoral heads, pubic bones, and heel. The coxa vara deformity of the hip joint is common.

It should be noted that x rays of individuals with spondyloepimetaphyseal dysplasia type Strudwick are virtually identical to congenital spondyloepiphyseal dysplasia. In early childhood, irregularity in the region beneath the ends of bones (metaphyseal) and thickening of the bones (sclerosis) are noted in spondyloepimetaphyseal dysplasia type Strudwick. Also, there is platyspondyly (flattened vertebral bodies) and odontoid hypoplasia.

Spondyloepiphyseal dysplasia tarda

Radiologic diagnosis cannot be established before 4-6 years of age. Symptoms usually begin to present between five and 10 years of age. Symptomatic changes in the spine and hips usually present between 10 and 14 years of age.

In adults, vertebral changes especially in the lumbar region, may be diagnostic. Ochronosis (pigment deposits in cartilage, ligaments, and tendons) is suggested by apparent intervertebral disc calcification, and the vertebral bodies are malformed and flattened with most of the dense area part of the vertebral plate.

Genetic counseling

Genetic counseling may be of benefit for patients and their families.

In congenital spondyloepiphyseal dysplasia, only one parent needs to be a carrier in order for the child to inherit the disorder. A child has a 50% chance of having the disorder if one parent has the disorder and a 75% chance of having the disease if both parents have congenital spondyloepiphyseal dysplasia.

In spondyloepiphyseal dysplasia tarda, if a mother has a male child, he has a 50% chance of inheriting the disease-causing gene. A male who inherits an X-linked recessive disorder is affected, and all of his daughters will be carriers, but none of his sons.

Prenatal testing

Prenatal testing may be available to couples at risk for bearing a child with spondyloepiphyseal dysplasia. Testing for the genes responsible for congenital spondyloepiphyseal dysplasia and spondyloepiphyseal dysplasia tarda is possible. Congenital spondyloepiphyseal dysplasia testing may be difficult, however, since although the gene has been located, there is variability in the mutations in the gene amongst persons with the disorder.

Either chorionic villus sampling (CVS) or **amniocentesis** may be performed for prenatal testing. CVS is a procedure to obtain chorionic villi tissue for testing. Examination of fetal tissue can reveal information about the defects that lead to spondyloepiphyseal dysplasia. Chorionic villus sampling can be performed at 10–12 weeks gestation.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus, into the amniotic sac, and withdrawing a small amount of amniotic fluid. **DNA** can be extracted from the fetal cells contained in the amniotic fluid and tested. Amniocentesis is performed at 16–18 weeks gestation.

Treatment and management

Individuals with spondyloepiphyseal dysplasia should be under routine health supervision by a physician who is familiar with the disorder, its complications, and its treatment.

Congenital spondyloepiphyseal dysplasia

Treatment is mostly symptomatic, and may include:

- Orthopedic care throughout life. Early surgical interventional may be needed to correct clubfoot and/or cleft palate. Hip, spinal, and knee complications may occur, and hip replacement is sometimes warranted in adults. Additionally, arthritis may develop due to poorly developed type II collagen. Spinal fusion may be indicated if evaluation of the cervical vertebrae C1 and C2 detects odontoid hypoplasia. If the odontoid is hypoplastic or small, it may predispose to instability and spinal cord compression in congenital spondyloepiphyseal dysplasia).

- Ophthalmologic examinations are important for the prevention of retinal detachment and treatment of myopia and early retinal tears if they occur.
- Hearing should be checked and ear infections should be closely monitored. Tubes may need to be placed in the ear.
- Due to neck instability, persons with SEDC should exercise caution to avoid activities/sports that could result in trauma to the neck or head.

Individuals with congenital spondyloepiphyseal dysplasia should be closely monitored during anesthesia and for complications during a respiratory infection. In particular, during anesthesia, special attention is required to avoid spinal injury resulting from lax ligaments causing instability in the neck. This condition may also result in spinal injury in contact sports and car accidents. Chest constriction may also cause decreased lung capacity.

Spondyloepiphyseal dysplasia tarda

Treatment is mostly symptomatic, and may include:

- Physical therapy to relieve joint stiffness and pain.
- Orthopedic care may be needed at different times throughout life. Bone changes of the femoral head often lead to secondary **osteoarthritis** during adulthood and some patients require total replacement of the hip before the age of 40 years.

Some individuals with short stature resulting from spondyloepiphyseal dysplasia may consider limb-lengthening surgery. This is a controversial surgery that lengthens leg and arm bones by cutting the bones, constructing metal frames around them, and inserting pins into them to move the cut ends apart. New bone tissue fills in the gap. While the surgery can be effective in lengthening limbs, various complications may occur.

Prognosis

Prognosis is variable dependent upon severity of the disorder. Generally, congenital spondyloepiphyseal dysplasia is more symptomatic than spondyloepiphyseal dysplasia tarda. Neither form of the disorder generally leads to shortened life span. Cognitive function is generally normal.

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ORGANIZATIONS

Human Growth Foundation. 997 Glen Cove Ave., Glen Head, NY 11545. (800) 451-6434. Fax: (516) 671-4055. <http://www. hgf1@hgfound.org>.

Little People of America, Inc. National Headquarters, PO Box 745, Lubbock, TX 79408. (806) 737-8186 or (888) LPA-2001. lpadatabase@juno.com. <http://www.lpaonline.org>.

Little People's Research Fund, Inc. 80 Sister Pierre Dr., Towson, MD 21204-7534. (410) 494-0055 or (800) 232-5773. Fax: (410) 494-0062. <http://pixelscapes.com/lprf>.

MAGIC Foundation for Children's Growth. 1327 N. Harlem Ave., Oak Park, IL 60302. (708) 383-0808 or (800) 362-4423. Fax: (708) 383-0899. mary@magicfoundation.org. <http://www.magicfoundation.org/ghd.html>.

Short Stature Foundation. 4521 Campus Drive, #310, Irvine, CA 92715. (714) 559-7131 or (800) 243-9273.

WEBSITES

OMIM—Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov/Omim/searchomim.html>.

Jennifer F. Wilson, MS

Spondyloepiphyseal dysplasia congenita

see **Spondyloepiphyseal dysplasia**

SRY (sex determining region Y)

Definition

The sex determining region Y (SRY) **gene** is located on the Y chromosome. SRY is the main genetic switch for the sexual development of the human male. If the SRY gene is present in a developing embryo, typically it will become male.

Description

The development of sex in a human depends on the presence or absence of an Y chromosome. **Chromosomes** are the structures in our cells that contain genes. Genes instruct the body on how to grow and develop by making proteins. For example, genes (and the proteins they make) are responsible for what color hair or eyes a person may have, how tall they will be, and what color skin they will have. Genes also direct the development of organs, such as the heart and brain. Genes are constructed

KEY TERMS

Cartilage—Supportive connective tissue which cushions bone at the joints or which connects muscle to bone.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

Epididymis—Coiled tubules that are the site of sperm storage and maturation for motility and fertility. The epididymis connects the testis to the vas deferens.

Gonad—The sex gland in males (testes) and females (ovaries).

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Nucleus—The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

Ovary—The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

Seminal vesicles—The pouches above the prostate that store semen.

Testes—The male reproductive organs that produce male reproductive cells (sperm) and male hormones.

Vas deferens—The long, muscular tube that connects the epididymis to the urethra through which sperm are transported during ejaculation.

out of **DNA**, deoxyribonucleic acid. DNA is found in the shape of a double helix, like a twisted ladder. The DNA contains the "letters" of the genetic code that make up the "words" or genes that govern the development of the body. The genes are found in the "books" or chromosomes in the cells.

Normally, there are 46 chromosomes, or 23 pairs, in each cell. The first 22 pairs are the same in men and women and are called the autosomes. The last pair, the sex chromosomes, consists of two X chromosomes in females (XX) and an X and an Y chromosome in males (XY). These 23 pairs of chromosomes contain approximately 35,000 genes.

Human males differ from human females in the fact that they have an Y chromosome and females do not. Scientists thought there must be a gene on the Y chromosome that is responsible for determining maleness. The gene for determining maleness was called TDF for testis determining factor. In 1990, the SRY gene was found and scientist believed it was the TDF gene they had been looking for. The evidence scientists had to show SRY was indeed TDF included the fact that is was located on the Y chromosome. When SRY was found in individuals with two X chromosomes (normally females) these individuals had male physical features. Furthermore, some individuals with XY sex chromosomes that had female physical features had mutations or alterations in their SRY gene. Finally, experiments were done on mice that showed a male mouse would develop when SRY was put into a chromosomally female embryo. This evidence proved that SRY is the TDF gene that triggers the pathway of a developing embryo to become male. While the SRY gene triggers the pathway to the development of a male, it is not the only gene responsible for sexual development. Most likely, the SRY gene serves to regulate the activity of other genes in this pathway.

Genetic profile

Men and women both have 23 pairs of chromosomes—22 pairs of autosomes and one pair of sex chromosomes (either XX in females or XY in males). The SRY gene is located on the Y chromosome. When a man and woman have a child, it is the man's chromosomes that determine if the baby will be male or female. This is because the baby inherits one of its sex chromosomes from the mother and one from the father. The mother has only X chromosomes to pass on, while the father can pass on either his X chromosome or his Y chromosome. If he passes on his X chromosome, the baby will be female. If he passes on his Y chromosome (with the SRY gene) the baby will be male. Statistically, each pregnancy has a 50% chance of being female and a 50% chance of being male. The Y chromosome is the smallest human chromosome and the SRY region contains a very small number of genes.

Signs and symptoms

Individuals with point mutations or deletions of the SRY gene have a condition known as gonadal dysgenesis, XY female type, also called Swyer syndrome. At birth the individuals with the XY female type of gonadal dysgenesis appear to be normal females (with female inner and outer genitalia), however, they do not develop secondary sexual characteristics at puberty, do not menstruate, and have "streak" (undeveloped) gonads. They

have normal stature and an increased incidence of certain neoplasms (gonadoblastoma and germinoma).

Normal development

In normal human sexual development, there are two stages called determination and differentiation. Determination occurs at conception when a sperm from a man fertilizes an egg from a woman. If the sperm has an Y chromosome, the conception will eventually become male. If no Y chromosome is present, the conception will become female.

Though the determination of sex occurs at conception, the differentiation of the developing gonads (future ovaries in the female and testes in the males) does not occur until about seven weeks. Until that time, the gonads look the same in both sexes and are called undifferentiated or indifferent. At this point in development, the embryo has two sets of ducts: the Mullerian ducts that form the fallopian tubes, uterus and upper vagina in females and the Wolffian ducts that form the epididymis, vas deferens, and seminal vesicles in males.

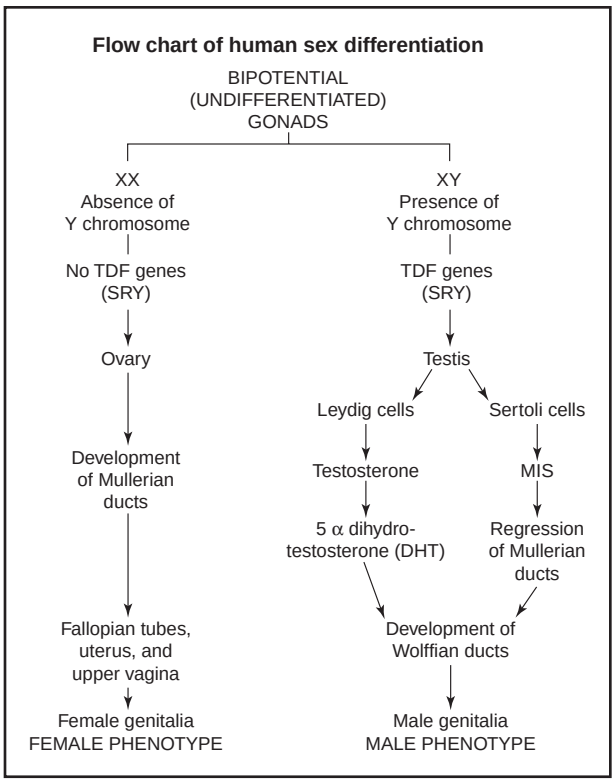
In embryos with SRY present, the undifferentiated gonads will develop into the male testes. The testes produce two hormones that cause the differentiation into maleness. Mullerian inhibiting substance (MIS), also called anti-mullerian hormone (AMH), causes the Mullerian ducts to regress and the Wolffian ducts develop into the internal male structures. Testosterone also helps with the development of the Wolffian ducts and causes the external genitals to become male.

When SRY is not present, the pathway of sexual development is shifted into female development. The undifferentiated gonads become ovaries. The Mullerian ducts develop into the internal female structures and the Wolffian ducts regress. The external genitals do not masculinize and become female.

SRY and male development

As of 2001, how the SRY gene causes an undifferentiated gonad to become a testis and eventually determine the maleness of a developing embryo is not completely understood. What scientists believe happens is that SRY is responsible for "triggering" a pathway of other genes that cause the gonad to continue to develop into a testis. The SRY protein is known to go into the nucleus of a cell and physically bend the DNA. This bending of DNA may allow other genes to be turned on that are needed in this pathway. For example, anti-Mullerian hormone is thought to be indirectly turned on by SRY.

It is also thought that a threshold exists that must be met at a very specific time for SRY to trigger this pathway. This means that enough SRY protein must be made early in development (before seven weeks) to turn an undifferentiated gonad into a testis. If enough SRY is not present or if it is present too late in development, the gonad will shift into the female pathway.



Flow chart of male and female sex differentiation from conception through development. *(Gale Group)*

Other genes in sex development

Several other genes have been found that are involved in the development of human sex, including the gene SOX9. Mutations or alterations in this gene can cause a condition called camptomelic **dysplasia**. People with camptomelic dysplasia have bone and cartilage changes. SOX9 alterations also cause male to female sex reversal in most affected individuals (male chromosomes and female features). As of 2001, it is not known how SRY, SOX9, and other genes in the sexual developmental pathway interact to turn an undifferentiated gonad into a testis or an ovary.

Resources

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Carin Lea Beltz, MS

Steinert disease *see* **Myotonic dystrophy**

Stein-Leventhal syndrome *see* **Polycystic ovary syndrome**

Stickler syndrome

Definition

Stickler syndrome is a disorder caused by a genetic malfunction in the tissue that connects bones, heart, eyes, and ears.

Description

Stickler syndrome, also known as hereditary arthro-ophthalmopathy, is a multisystem disorder that can affect the eyes and ears, skeleton and joints, and craniofacies. Symptoms may include **myopia**, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial underdevelopment and cleft palate; and mild **spondyloepiphyseal dysplasia** and/or arthritis. The collection of specific symptoms that make up the syndrome were first documented by Stickler et al., in a 1965 paper published in *Mayo Clinic Proceedings* titled "Hereditary Progressive Arthro-Opthalmopathy." The paper associated the syndrome's sight deterioration and joint changes. Subsequent research has redefined Stickler syndrome to include other symptoms.

Genetic profile

Stickler syndrome is associated with mutations in three genes: COL2A1 (chromosomal locus 12q13), COL11A1 (chromosomal locus 1p21), and COL11A2 (chromosomal locus 6p21). It is inherited in an autosomal dominant manner. The majority of individuals with Stickler syndrome inherited the abnormal allele from a parent, and the prevalence of new gene mutations is unknown. Individuals with Stickler syndrome have a 50% chance of passing on the abnormal gene to each offspring.

The syndrome can manifest itself differently within families. If the molecular genetic basis of Stickler syndrome has been established, molecular **genetic testing** can be used for clarification of each family member's genetic status and for prenatal testing.

A majority of cases are attributed to COL2A1 mutations. All COL2A1 mutations known to cause Stickler syndrome result in the formation of a premature termination codon within the type-II collagen gene. Mutations in COL11A1 have only recently been described, and COL11A2 mutations have been identified only in patients lacking ocular findings.

Although the syndrome is associated with mutations in the COL2A1, COL11A1, and COL11A2 genes, no linkage to any of these three known loci can be established in some rare cases with clinical findings consistent with Stickler syndrome. It is presumed that other, as yet unidentified, genes mutations also account for Stickler syndrome.

Genetically related disorders

There are a number of other phenotypes associated with mutations in COL2A1. **Achondrogenesis** type I is a fatal disorder characterized by absence of bone formation in the vertebral column, sacrum, and pubic bones, by the shortening of the limbs and trunk, and by prominent abdomen. Hypochondrogenesis is a milder variant of achondrogenesis. Spondyloepiphyseal **dysplasia** congenita, a disorder with skeletal changes more severe than in Stickler syndrome, manifests in significant short stature, flat facial profile, myopia, and vitreoretinal degeneration. Spondyloepimetaphyseal dysplasia Strudwick type is another skeletal disorder that manifests in severe short stature with severe protrusion of the sternum and **scoliosis**, cleft palate, and retinal detachment. A distinctive radiographic finding is irregular sclerotic changes, described as dappled, which are created by alternating zones of osteosclerosis and ostopenia in the metaphyses (ends) of the long bones. Spondyloperipheral dysplasia is a rare condition characterized by short stature and radiographic changes consistent with a spondyloepiphyseal dysplasia and **brachydactyly.** Kneist dysplasia is a disorder that manifests in disproportionate short stature, flat facial profile, myopia and vitreoretinal degeneration, cleft palate, backward and lateral curvature of the spine, and a variety of radiographic changes.

Other phenotypes associated with mutations in COL11A1 include **Marshall syndrome**, which manifests in ocular hypertelorism, hypoplasia of the maxilla and nasal bones, flat nasal bridge, and small upturned nasal tip. The flat facial profile of Marshall syndrome is usually evident into adulthood, unlike Stickler syndrome.

Manifestations include radiographs demonstrating hypoplasia of the nasal sinuses and a thickened calvarium. Ocular manifestations include high myopia, fluid vitreous humor, and early onset cataracts. Sensorineural hearing loss is common and sometimes progressive. Cleft palate is seen both as isolated occurrence and as part of the Pierre-Robin sequence (micrognathia, cleft palate, and glossoptosis). Other manifestations include short stature and early onset arthritis, and skin manifestations that may include mild hypotrichosis and hypohidrosis.

Other phenotypes associated with mutations in COL11A2 include autosomal recessive oto-spondylometa-epiphyseal dysplasia, a disorder characterized by flat facial profile, cleft palate, and severe hearing loss. Anocular Stickler syndrome caused by COL11A2 mutations is close in similarity to this disorder. Weissenbach-Zweymuller syndrome has been characterized as neonatal Stickler syndrome but it is a separate entity from Stickler syndrome. Symptoms include midface hypoplasia with a flat nasal bridge, small upturned nasal tip, micrognathia, sensorineural hearing loss, and rhizomelic limb shortening. Radiographic findings include vertebral coronal clefts and dumbbell-shaped femora and humeri. Catch-up growth after age two or three is common and the skeletal findings become less apparent in later years.

KEY TERMS

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Dysplasia—The abnormal growth or development of a tissue or organ.

Glossoptosis—Downward displacement or retraction of the tongue.

Micrognathia—Small lower jaw with recession of lower chin.

Mitral valve prolapse—A heart defect in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur but there are usually no symptoms.

Otitis media—Inflammation of the middle ear, often due to fluid accumulation secondary to an infection.

Phenotype—The physical expression of an individuals genes.

Spondyloepiphyseal dysplasia—Abnormality of the vertebra and epiphyseal centers that causes a short trunk.

Demographics

No studies have been done to determine Stickler syndrome prevalence. An approximate incidence of Stickler syndrome among newborns is estimated based on data on the incidence of Pierre-Robin sequence in newborns. One in 10,000 newborns have Pierre-Robin sequence, and 35% of these newborns subsequently develop signs or symptoms of Stickler syndrome. These data suggest that the incidence of Stickler syndrome among neonates is approximately one in 7,500.

Signs and symptoms

Stickler syndrome may affect the eyes and ears, skeleton and joints, and craniofacies. It may also be associated with coronary complications.

Ocular symptoms

Near-sightedness is a common symptom of Stickler syndrome. High myopia is detectable in newborns. Common problems also include astigmatism and cataracts. Risk of retinal detachment is higher than normal. Abnormalities of the vitreous humor, the colorless, transparent jelly that fills the eyeball, are also observed. Type 1, the more common vitreous abnormality, is characterized by a persistence of a vestigial vitreous gel in the space behind the lens, and is bordered by a folded membrane. Type 2, which is much less common, is characterized by sparse and irregularly thickened bundles throughout the vitreous cavity. These vitreous abnormalities can cause sight deterioration.

Auditory symptoms

Hearing impairment is common, and some degree of sensorineural hearing loss is found in 40% of patients. The degree of hearing impairment is variable, however, and may be progressive. Typically, the impairment is high tone and often subtle. Conductive hearing loss is also possible. It is known that the impairment is related to the expression of type II and IX collagen in the inner ear, but the exact mechanism for it is unclear. Hearing impairment may be secondary to the recurrent ear infections often associated with cleft palate, or it may be secondary to a disorder of the ossicles of the middle ear.

Skeletal symptoms

Skeletal manifestations are short stature relative to unaffected siblings, early-onset arthritis, and abnormalities at ends of long bones and vertebrae. Radiographic

findings consistent with mild spondyloepiphyseal dysplasia. Some individuals have a physique similar to **Marfan syndrome**, but without tall stature. Young patients may exhibit joint laxity but it diminishes or even resolves completely with age. Early-onset arthritis is common and generally mild, mostly resulting in joint stiffness. Arthritis is sometimes severe, leading to joint replacement as early as the third or fourth decade.

Craniofacial findings

Several facial features are common with Stickler syndrome. A flat facial profile referred to as a "scooped out" face results from underdevelopment of the maxilla and nasal bridge, which can cause telecanthus and epicanthal folds. Flat cheeks, flat nasal bridge, small upper jaw, pronounced upper lip groove, small lower jaw, and palate abnormalities are possible, all in varying degrees. The nasal tip may be small and upturned, making the groove in the middle of the upper lip appear long. Micrognathia is common and may compromise the upper airway, necessitating tracheostomy. Midfacial hypoplasia is most pronounced in infants and young children, and older individuals may have a normal facial profile.

Coronary findings

Mitral valve prolapse may be associated with Stickler syndrome, but studies are, as yet, inconclusive about the connection.

Diagnosis

Stickler is believed to be a common syndrome in the United States and Europe, but only a fraction of cases are diagnosed since most patients have minor symptoms. Misdiagnosis may also occur because symptoms are not correlated as having a single cause. More than half of patients with Stickler syndrome are originally misdiagnosed according to one study.

While the diagnosis of Stickler syndrome is clinically based, clinical diagnostic criteria have not been established. Patients usually do not have all symptoms attributed to Stickler syndrome. The disorder should be considered in individuals with clinical findings in two or more of the following categories:

- Ophthalmologic. Congenital or early-onset cataract, myopia greater than -3 diopters, congenital vitreous anomaly, rhegmatogenous retinal detachment. Normal newborns are typically hyperopic (+1 diopter or greater), and so any degree of myopia in an at-risk newborn, such as one with Pierre-Robin sequence or an affected parent, is suggestive of the diagnosis of Stickler syndrome. Less common ophthalmological symptoms include paravascular pigmented lattice degeneration and cataracts.
- Craniofacial. Midface hypoplasia, depressed nasal bridge in childhood, anteverted nares (tipped or bent nasal cavity openings), split uvula, cleft hard palate, micrognathia, Pierre-Robin sequence.
- Audiologic. Sensorineural hearing loss.
- Joint. Hypermobility, mild spondyloepiphyseal dysplasia, precocious osteoarthritis.

It is appropriate to evaluate at-risk family members with a medical history and physical examination and ophthalmologic, audiologic, and radiographic assessments. Childhood photographs may be helpful in the evaluation of adults since craniofacial findings may become less distinctive with age.

Molecular genetic testing

Mutation analysis for COL2A1, COL11A1, and COL11A2 is available. Detection is performed by mutation scanning of the coding sequences. Stickler syndrome has been associated with stop mutations in COL2A1 and with missense and splicing mutations in all of the three genes. Because the meaning of a specific missense mutation within the gene coding sequence may not be clear, mutation detection in a parent is not advised without strong clinical support for the diagnosis.

Clinical findings can influence the order for testing the three genes. In patients with ocular findings, including type 1 congenital vitreous abnormality and mild hearing loss, COL2A1 may be tested first. In patients with typical ocular findings including type 2 congenital vitreous anomaly and significant hearing loss, COL11A1 may be tested first. In patients with hearing loss and craniofacial and joint manifestations but without ocular findings, COL11A2 may be tested first.

Prenatal testing

Before considering prenatal testing, its availability must be confirmed and prior testing of family members is usually necessary. Prenatal molecular genetic testing is not usually offered in the absence of a known disease-causing mutation in a parent. For fetuses at 50% risk for Stickler syndrome, a number of options for prenatal testing may exist. If an affected parent has a mutation in the gene COL2A1 or COL11A1, molecular genetic testing may be performed on cells obtained by chorionic villus sampling at 10–12 weeks gestation or **amniocentesis** at 16–18 weeks gestation. Alternatively, or in conjunction with molecular genetic testing, ultrasound examination can be performed at 19–20 weeks gestation to detect cleft palate. For fetuses with no known family history of Stickler syn-

drome in which cleft palate is detected, a three-generation pedigree may be obtained, and relatives who have findings suggestive of Stickler syndrome should be evaluated.

Treatment and management

Individuals diagnosed with Stickler syndrome, and individuals in whom the diagnosis cannot be excluded, should be followed for potential complications.

Evaluation by an ophthalmologist familiar with the ocular manifestations of Stickler syndrome is recommended. Individuals with known ocular complications may prefer to be followed by a vitreoretinal specialist. Patients should avoid activities that may lead to traumatic retinal detachment, such as contact sports. Patients should be advised of the symptoms associated with a retinal detachment and the need for immediate evaluation and treatment when such symptoms occur. Individuals from families with Stickler syndrome and a known COL2A1 or COL11A1 mutation who have not inherited the mutant allele do not need close ophthalmologic evaluation.

A baseline audiogram to test hearing should be performed when the diagnosis of Stickler syndrome is suspected. Follow-up audiologic evaluations are recommended in affected persons since hearing loss can be progressive.

Radiological examination may detect signs of mild spondyloepiphyseal dysplasia. Treatment is symptomatic, and includes over-the-counter anti-inflammatory medications before and after physical activity. No preventative therapies currently exist to minimize joint damage in affected individuals. In an effort to delay the onset of arthropathy, physicians may recommend avoiding physical activities that involve high impact to the joints, but no data support this recommendation.

Infants with Pierre-Robin sequence need immediate attention from otolaryngology and pediatric critical care specialists. Evaluation and management in a comprehensive craniofacial clinic that provides all the necessary services, including otolaryngology, plastic surgery, oral and maxillofacial surgery, pediatric dentistry, and orthodontics is recommended. Tracheostomy may be required, which involves placing a tube in the neck to facilitate breathing.

Middle ear infections may be a recurrent problem secondary to the palatal abnormalities, and ear tubes may be required. Micrognathia (small jaw) tends to become less prominent over time in most patients, allowing for removal of the tracheostomy. In some patients, however, significant micrognathia persists and causes orthodontic problems. In these patients, a mandibular advancement procedure may be required to correct jaw misalignment.

Cardiac care is recommended if complaints suggestive of mitral valve prolapse, such as episodic tachycardia and chest pain, are present. While the prevalence of mitral valve prolapse in Stickler syndrome is unclear, all affected individuals should be screened since individuals with this disorder need antibiotic prophylaxis for certain surgical procedures.

Prognosis

Prognosis is good under physician care. It is particularly important to receive regular vision and hearing exams. If retinal detachment is a risk, it may be advisable to avoid contact sports. Some craniofacial symptoms may improve with age.

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ORGANIZATIONS

Stickler Involved People. 15 Angelina, Augusta, KS 67010. (316) 775-2993. <http://www.sticklers.org>.

Stickler Syndrome Support Group. PO Box 371, Walton-on-Thames, Surrey KT12 2YS, England. 44-01932 267635. <http://www.stickler.org.uk>.

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Robin, Nathaniel H., and Matthew L. Warman. “Stickler Syndrome.” *GeneClinics.* University of Washington, Seattle. <http://www.geneclinics.org/profiles/stickler>.

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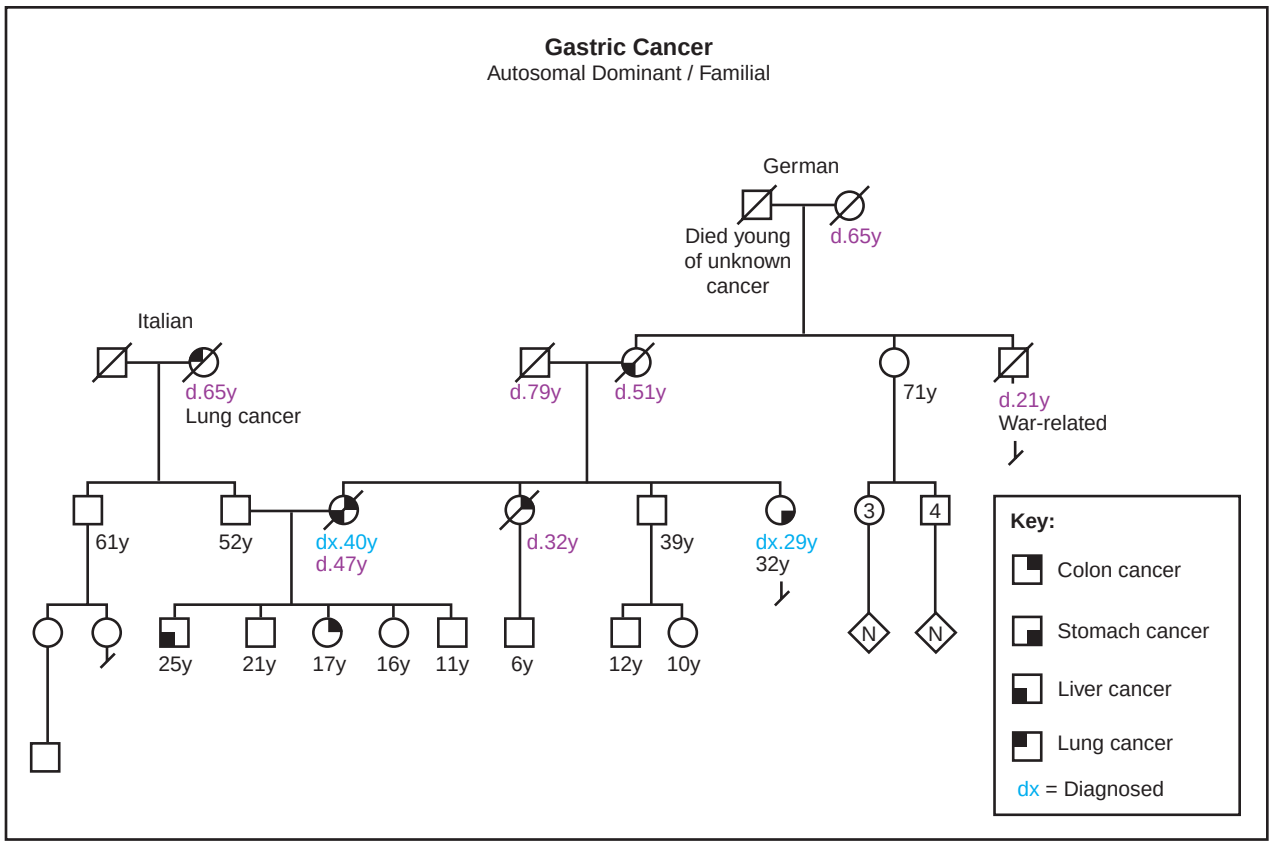
Jennifer F. Wilson, MS

Stomach cancer

Definition

Stomach cancer (also known as gastric cancer) is a disease in which the cells forming the inner lining of the



(Gale Group)

stomach become abnormal and start to divide uncontrollably, forming a mass or a tumor.

Description

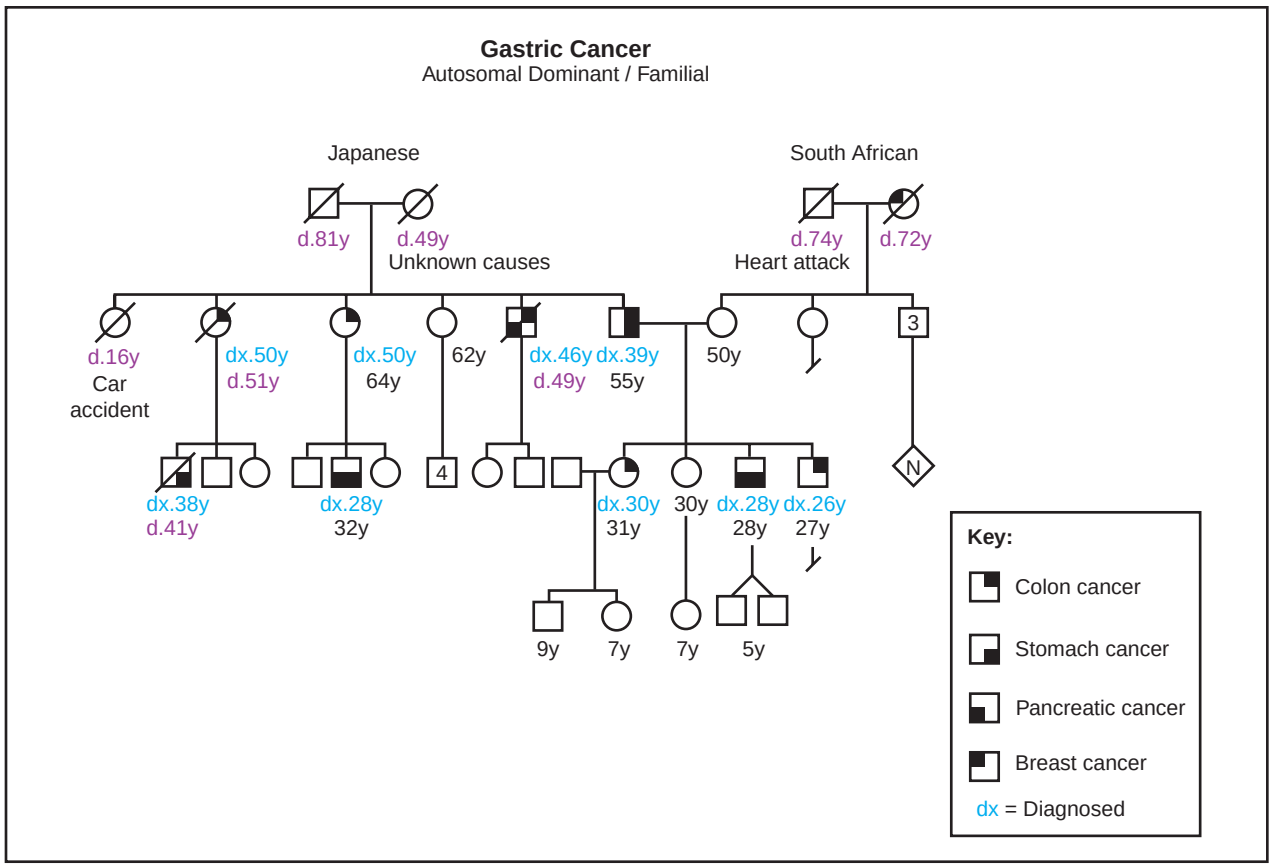
The stomach is a J-shaped organ that lies in the abdomen, on the left side. The esophagus (or the food pipe) carries the food from the mouth to the stomach. The stomach produces many digestive juices and acids that mix with the food and aid in the process of digestion. The stomach is divided into five sections. The first three are together referred to as the proximal stomach, and produce acids and digestive juices, such as pepsin. The fourth section of the stomach is where the food is mixed with the gastric juices. The fifth section of the stomach acts as a valve and controls the emptying of the stomach contents into the small intestine. The fourth and the fifth sections together are referred to as the distal stomach. Cancer can develop in any of the five sections of the stomach. The symptoms and the outcomes of the disease may vary depending on the location of the cancer.

In many cases, the cause of the stomach cancer is unknown. Several environmental factors have been linked to stomach cancer. Consuming large amounts of smoked, salted, or pickled foods has been linked to increased stomach cancer risk. Nitrates and nitrites, chemicals found in some foods such as cured meats may be linked to stomach cancer as well.

Infection by the *Helicobacter pylori* (*H. pylori*) bacterium has been found more often in people with stomach cancer. *H. pylori* can cause irritation of the stomach lining (chronic atrophic gastritis), which may lead to precancerous changes of the stomach cells.

People who have had previous stomach surgery for ulcers or other conditions may have a higher likelihood of developing stomach cancers, although this is not certain. Another risk factor is developing polyps, benign growths in the lining of the stomach. Although polyps are not cancerous, some may have the potential to turn cancerous.

While no particular **gene** for stomach cancer has yet been identified, people with blood relatives who have been diagnosed with stomach cancer are more likely to develop the disease. In addition, people who have inherited disorders such as familial adenomatous polyps (FAP) and Lynch syndrome have an increased risk for stomach cancer. For unknown reasons, stomach cancers occur more frequently in people with the blood group A.



(Gale Group)

Genetic profile

Although environmental or health factors may explain frequent occurrences of stomach cancer in families, it is known that inherited risk factors also exist. Some studies show close relatives having an increased risk of stomach cancer two to three times that of the general population. Interestingly, an earlier age at the time of stomach cancer diagnosis may be more strongly linked to familial stomach cancer. Two Italian studies estimated that about 8% of stomach cancer is due to inherited factors. Some of these hereditary factors are known genetic conditions while in other instances, the factors are unknown.

Familial cancer syndromes are hereditary conditions in which specific types of cancer, and perhaps other features, are consistently occurring in affected individuals. Familial adenomatosis (FAP) and hereditary nonpolyposis colon cancer (HNPCC) are familial cancer syndromes that increase the risk of colon cancer.

FAP is due to changes in the *APC* gene. Individuals with FAP typically have more than 100 polyps, mushroom-like growths, in the digestive system as well as other effects. Polyps are noncancerous growths that have the potential to become cancerous if not removed. At least one study estimated that the risk of stomach cancer was seven times greater for individuals with FAP than the general population.

The number of polyps present is an important distinction between FAP and HNPCC. Polyps do not form at such a high rate in HNPCC but individuals with this condition are still at increased risk of colon, gastric, and other cancers. At least five genes are known to cause HNPCC, but alterations in the *hMSH2* or *hMLH1* genes have been found in the majority of HNPCC families.

Other inherited conditions such as Peutz-Jeghers, Cowden and Li-Fraumeni syndromes and other syndromes have been associated with stomach cancer. All of these syndromes have distinct features beyond stomach cancer that aid in identifying the specific syndrome. The **inheritance** pattern for most of these syndromes is dominant, meaning only one copy of the gene needs to be inherited for the syndrome to be present.

In 1999, the First Workshop of the International Gastric Cancer Linkage Consortium developed criteria for defining hereditary stomach cancer not due to

known genetic conditions, such as those listed above. In areas with low rates of stomach cancer, hereditary stomach cancer was defined according to the Consortium as: (1) families with two or more cases of stomach cancer in first or second degree relatives (siblings, parents, children, grandparents, nieces/nephews or aunts/uncles) with at least one case diagnosed before age 50 or (2) three or more cases at any age. In countries with higher rates of stomach cancer, such as Japan, the suggested criteria are: (1) at least three affected first degree relatives (sibling, children or parents) and one should be the first degree relative of the other two; (2) at least two generations (without a break) should be affected; and (3) at least one cancer should have occurred before age 50.

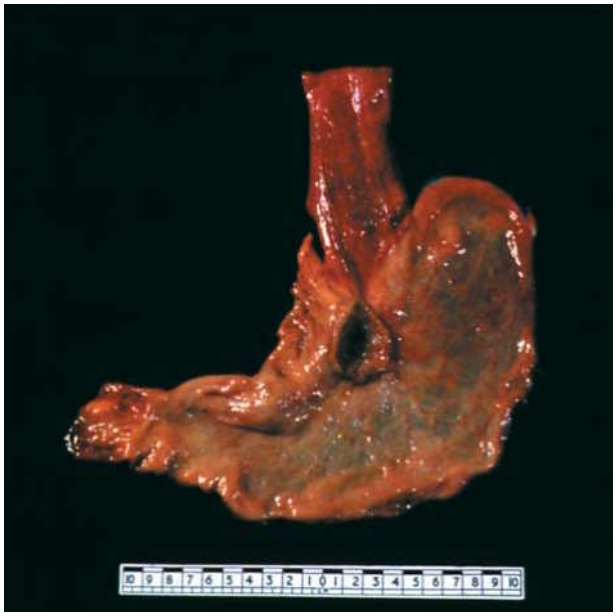
Inherited changes in the *E-Cadherin/CDH1* gene first were reported in three families of native New Zealander (Maori) descent with stomach cancer and later were found in families of other ancestry. The E-Cadherin/CDH1 gene, which plays a role in cell to cell connection, is located on chromosome 16 at 16q22. The percentage of hereditary stomach cancer that is due to E-Cadherin/CDH1 gene alterations is uncertain. In summary, most stomach cancer is due to environmental or other non-genetic causes. A small portion of cancer of the stomach, about 8%, is due to inherited factors one of which is E-Cadherin/CDH1 gene alterations.

Demographics

The American Cancer Society estimates, based on previous data from the National Cancer Institute and the United States Census, that 21,700 Americans will be diagnosed with stomach cancer during 2001. In some areas, nearly twice as many men are affected by stomach cancer than women. Most cases of stomach cancer are diagnosed between the ages of 50 and 70 but in families with a hereditary risk of stomach cancer, younger cases are more frequently seen. Stomach cancer is one of the leading causes of cancer deaths in many areas of the world, most notably Japan, but the number of new stomach cancer cases is decreasing in some areas, especially in developed countries. In the United States, the use of refrigerated foods and increased consumption of fresh fruits and vegetables, instead of preserved foods, may be a reason for the decline in stomach cancer.

Signs and symptoms

Stomach cancer can be difficult to detect at early stages since symptoms are uncommon and frequently unspecific. The following can be symptoms of stomach cancer:



An excised specimen of a human stomach showing a cancerous tumor (triangular shaped). *(Custom Medical Stock Photo, Inc.)*

- poor appetite or weight loss
- fullness even after a small meal
- abdominal pain
- heart burn, belching, indigestion or nausea
- vomiting, with or without blood
- swelling or problems with the abdomen
- anemia or blood on stool (feces) examination

Diagnosis

In addition to a physical examination and fecal occult blood testing (checking for blood in the stool), special procedures are done to evaluate the digestive system including the esophagus, stomach, and upper intestine. Procedures used to diagnose stomach cancer include: barium upper gastrointestinal (GI) x rays, upper endoscopy, and endoscopic ultrasound. **Genetic testing** can also be used to determine an individuals predisposition to stomach cancer.

Upper GI x rays

The first step in evaluation for stomach cancer may be x ray studies of the esophagus, stomach, and upper intestine. This type of study requires drinking a solution with barium to coat the stomach and other structures for easier viewing. Air is sometimes pumped into the stomach to help identify early tumors.

Upper endoscopy

Endoscopy allows a diagnosis in about 95% of cases. In upper endoscopy, a small tube, an endoscope, is placed down the throat so that the esophagus, stomach, and upper small intestine can be viewed. If a suspicious area is seen, a small sample of tissue, a biopsy, is taken. The tissue from these samples can be examined for evidence of cancer.

Endoscopic ultrasound

Endoscopic ultrasound allows several layers to be seen and so it is useful in determining where cancer may have spread. With this test, an endoscope is placed into the stomach and sound waves are emitted. A machine analyzes the sound waves to see differences in the tissues in order to identify tumors.

Genetic testing

If a certain genetic syndrome such as FAP or HNPCC is suspected, genetic testing may be available either through a clinical laboratory or through a research study. As of 2001, testing for E-cadherin/CDH1 gene alterations is mainly available through research studies. Once an E-cadherin/CDH1 gene change is identified through research, the results can be confirmed through a certified laboratory.

When a gene change is identified, genetic testing may be available for other family members. For most genetic tests, it is helpful to test the affected individual first, since they are most likely to have a gene change. Genetic testing is usually recommended for consenting adults, however, for syndromes in which stomach cancer is a common feature, testing of children may be reasonable for possible prevention of health problems.

The detection rate and usefulness of genetic testing depends on the genetic syndrome. If genetic testing is under consideration, a detailed discussion with a knowledgeable physican, genetic counselor, or other practitioner is helpful in understanding the advantages and disadvantages of the genetic test. It is also important to realize that testing positive for the E-cadherin/CDH1 gene does not necessarily mean the individual will be affected with cancer. However, they may have an increased risk compared to an individual without the gene.

Treatment and management

Regular mass screening for stomach cancer has not been found useful in areas, such as the United States, where stomach cancer is less common. When stomach cancer is diagnosed in the United States, it is usually discovered at later, less curable stages. However, individuals with an increased risk of stomach cancer, including those with a known genetic syndrome or with a family history of the disease, may consider regular screening before the development of cancer. If a known hereditary cancer syndrome is suspected, screening should follow the generally accepted guidelines for these conditions.

In 1999, the First Workshop of the International Gastric Cancer Linkage Consortium recommended that regular detailed upper endocopy and biopsy be done in families with hereditary stomach cancer, including screening every six to 12 months for individuals with known E-cadherin gene alterations, if no other treatment has been done. Some individuals with a known hereditary stomach cancer risk have surgery to remove the stomach prior to development of any stomach cancer, but the effectiveness of this prevention strategy is uncertain. Several other less drastic prevention measures have been considered including changes in diet, use of vitamins, and antibiotic treatment of *H. pylori*. The American Cancer Society recommends limiting use of alcohol and tobacco.

Treatment of stomach cancer, in nearly all cases, involves some surgery. The amount of the stomach or surrounding organs that is removed depends on the size and location of the cancer. Sometimes, surgery is performed to try to remove all of the cancer in hopes of a cure while other times, surgery is done to relieve symptoms. Possible side effects of stomach surgery include leaking, bleeding, changes in diet, vitamin deficiencies, and other complications.

Chemotherapy involves administering anti-cancer drugs either intravenously (through a vein in the arm) or orally (in the form of pills). This can either be used as the primary mode of treatment or after surgery to destroy any cancerous cells that may have migrated to distant sites. Side effects (usually temporary) of chemotherapy may include low blood counts, hair loss, vomiting, and other symptoms.

Radiation therapy is often used after surgery to destroy the cancer cells that may not have been completely removed during surgery. Generally, to treat stomach cancer, external beam radiation therapy is used. In this procedure, high-energy rays from a machine that is outside of the body are concentrated on the area of the tumor. In the advanced stages of stomach cancer, radiation therapy is used to ease the symptoms such as pain and bleeding.

Prognosis

"Staging" is a method of describing cancer development. There are five stages in stomach cancer with stage 0 being the earliest cancer that has not spread while stage IV includes cancer that has spread to other organs.

Expected survival rate can be roughly estimated based on the stage of cancer at the time of diagnosis.

The prognosis for patients with early stage cancer depends on the location of the cancer. When cancer is in the proximal part of the stomach, only 10-15% of people survive five years or more, even if they have been diagnosed with early stage cancer. For cancer that is in the distal part of the stomach, if it is detected at an early stage, the outlook is somewhat better. About 50% of the people survive for at least five years or more after initial diagnosis. However, only 20% of the patients are diagnosed at an early stage. Chance of survival depends on many factors and it is difficult to predict survival for a particular individual.

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National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

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Kristin Baker Niendorf, MS, CGC

Sturge-Weber syndrome

Definition

Sturge-Weber syndrome (SRS) is a condition involving specific brain changes that often cause seizures and mental delays. It also includes port-wine colored birthmarks (or "port-wine stains"), usually found on the face.

KEY TERMS

Calcification—A process in which tissue becomes hardened due to calcium deposits.

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Leptomeningeal angioma—A swelling of the tissue or membrane surrounding the brain and spinal cord, which can enlarge with time.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Port-wine stain—Dark-red birthmarks seen on the skin, named after the color of the dessert wine.

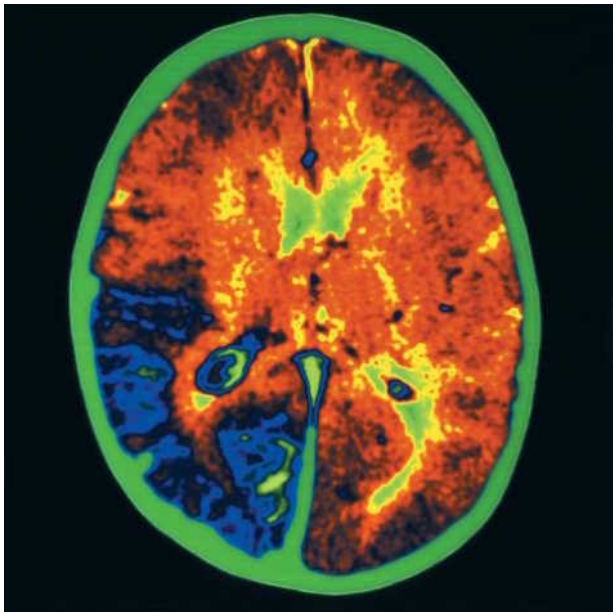
Sclera—The tough white membrane that forms the outer layer of the eyeball.

Description

The brain finding in SRS is leptomeningeal angioma, which is a swelling of the tissue surrounding the brain and spinal cord. These angiomas cause seizures in approximately 90% of people with SWS. A large number of affected individuals are also mentally delayed.

Port-wine stains are present at birth. They can be quite large, and are typically found on the face near the eyes or on the eyelids. Vision problems are common, especially if a port-wine stain covers the eyes. These vision problems can include **glaucoma** and vision loss.

Facial features, such as port-wine stains, can be very challenging for individuals with SWS. These birthmarks can increase in size with time, and this may be particularly emotionally distressing for the individuals, as well as their parents. A state of unhappiness about this is more common during middle childhood and later than it is at younger ages.



This magnetic resonance image of the brain shows a patient affected with Sturge-Weber syndrome. The front of the brain is at the top. Green colored areas indicate fluid-filled ventricles. The blue area is where the brain has become calcified. *(Photo Researchers, Inc.)*

Genetic profile

The genetics behind Sturge-Weber syndrome are still unknown. Interestingly, in other genetic conditions involving changes in the skin and brain (such as **neurofibromatosis** and **tuberous sclerosis**) the genetic causes are well described. It is known that most people with SRS are the only ones in their family with the condition; there is usually not a strong family history of the disease. However, as of 2001 a **gene** known to cause SRS is still not known. For now, SRS is thought to be caused by a random, sporadic event.

Demographics

Sturge-Weber syndrome is a sporadic disease that is found throughout the world, affecting males and females equally. The total number of people with Sturge-Weber syndrome is not known, but estimates range between one in 400,000 to one in 40,000.

Signs and symptoms

People with SWS may have a larger head circumference (measurement around the head) than usual. Leptomeningeal angiomas can progress with time. They usually only occur on one side of the brain, but can exist on both sides in up to 30% of people with SWS. The angiomas can also cause great changes within the brain's white matter. Generalized wasting, or regression, of portions of the brain can result from large angiomas. Calcification of the portions of the brain underlying the angiomas can also occur. The larger and more involved the angiomas are, the greater the expected amount of mental delays in the individual. Seizures are common in SWS, and they can often begin in very early childhood. Occasionally, slight paralysis affecting one side of the body may occur.

Port-wine stains are actually capillaries (blood vessels) that reach the skin's surface and grow larger than usual. As mentioned earlier, the birthmarks mostly occur near the eyes; they often occur only on one side of the face. Though they can increase in size over time, port-wine stains cause no direct health problems for the person with SWS.

Vision loss and other complications are common in SWS. The choroid of the eye can swell, and this may lead to increased pressure within the eye in 33-50% of people with SWS. Glaucoma is another common vision problem seen in SWS, and is more often seen when a person has a port-wine stain that is near or touches the eye.

In a 2000 study about the psychological functioning of children with SRS, it was noted that parents and teachers report a higher incidence of social problems, emotional distress, and problems with compliance in these individuals. Taking the mental delays into account, behaviors associated with **attention-deficit hyperactivity disorder** (ADHD) were noted; as it turns out, about 22% of people with SWS are eventually diagnosed with ADHD.

Diagnosis

Because no **genetic testing** is available for Sturge-Weber syndrome, all diagnoses are made through a careful physical examination and study of a person's medical history.

Port-wine stains are present at birth, and seizures may occur in early childhood. If an individual has both of these features, SWS should be suspected. A brain MRI or CT scan can often reveal a leptomeningeal angioma, brain calcifications, as well as any other associated white matter changes.

Treatment and management

Treatment of seizures in SWS by anti-epileptic medications is often an effective way to control them. In the rare occasion that an aggressive seizure medication therapy is not effective, surgery may be necessary. The general goal of the surgery is to remove the portion of brain that is causing the seizures, while keeping the normal brain tissue intact. Though most patients with SWS only have brain

surgery as a final attempt to treat seizures, some physicians favor earlier surgery because this may prevent some irreversible damage to the brain (caused by the angiomas).

Standard glaucoma treatment, including medications and surgery, is used to treat people with this complication. This can often reduce the amount of vision loss.

There is no specific treatment for port-wine stains. Because they contain blood vessels, it could disrupt blood flow to remove or alter the birthmarks.

Prognosis

The prognosis for people with SWS is directly related to the amount of brain involvement for the leptomeningeal angiomas. For those individuals with smaller angiomas, prognosis is relatively good, especially if they do not have severe seizures or vision problems.

Resources

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ORGANIZATIONS

The Sturge-Weber Foundation. PO Box 418, Mount Freedom, NJ 07970. (800) 627-5482 or (973) 895-4445. Fax: (973) 895-4846. swfoffice@aol.com. <http://www.sturgeweber.com/>.

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Deepti Babu, MS

Summitt syndrome *see* **Carpenter syndrome**

Surdicardiac syndrome *see* **Jervell and Lange-Nielsen syndrome**

Sutherland-Haan syndrome

Definition

Sutherland-Haan syndrome is an inherited X-linked disorder characterized by mental retardation, small head circumference, small testes, and spastic diplegia. Grant Sutherland and co-workers first described the syndrome in 1988. At present, it has only been fully described in one single, large, Australian family. Thus, it is unknown if the disorder occurs worldwide or only in certain ethnic and racial groups. Since the responsible **gene** is located on the X chromosome, Sutherland-Haan syndrome is exclusively found in males. As the gene is unknown and only one family has been described (although there are families suspected of having Sutherland-Haan) the prevalence is unknown.

KEY TERMS

Microcephaly—An abnormally small head.

Short stature—Shorter than normal height, can include dwarfism.

Small testes—Refers to the size of the male reproductive glands, located in the cavity of the scrotum.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

X-linked mental retardation—Subaverage general intellectual functioning that originates during the developmental period and is associated with impairment in adaptive behavior. Pertains to genes on the X chromosome.

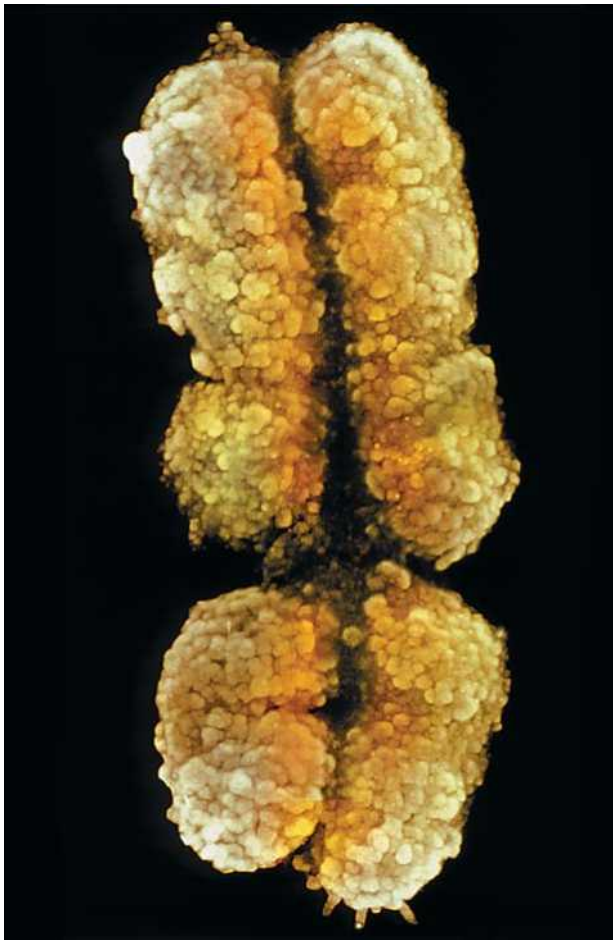
Description

Sutherland-Haan syndrome is among the group of **genetic disorders** known as X-linked mental retardation (XLMR) syndromes. Manifestations in males may be present prior to birth, as intrauterine growth appears to be mildly impaired since birth weight is below normal. Similarly, postnatal growth is slow with the head circumference being quite small (microcephaly) and height being rather short. Affected males exhibit poor feeding during infancy. Additionally, affected males have small testes after puberty.

The diagnosis is very difficult especially if there is no family history of mental retardation. If there is a family history of mental retardation and if the **inheritance** pattern is consistent with X-linkage, then the diagnosis is possible based on the presence of the above clinical findings and localization to Xp11.3 to Xq12.

Genetic profile

Sutherland-Haan syndrome is caused by an alteration in an unknown gene located in the pericentric region (area flanking the centromere) of the X chromosome. The altered gene in affected males is most likely inherited from a carrier mother. As males have only one X chromosome, a



Sutherland Haan syndrome is a form of mental retardation linked to a gene abnormality on the X chromosome. *(Photo Researchers, Inc.)*

mutation in an X-linked gene is fully expressed in males. On the other hand, as carrier females have a normal, second X-chromosome, they do not exhibit any of the phenotype associated with Sutherland-Haan syndrome.

Female carriers have a 50/50 chance of transmitting the altered gene to a daughter or a son. A son with the altered gene will be affected but will likely not reproduce.

Demographics

Only males are affected with Sutherland-Haan syndrome. Carrier females exhibit none of the phenotypic features. Although Sutherland-Haan has only been reported in a single Australian family, there is no reason to assume it is not present in other racial/ethnic groups.

Signs and symptoms

Evidence of Sutherland-Haan syndrome is present at birth as affected males have below normal birth weight. This may reflect mildly impaired intrauterine growth. Postnatal growth is also slow. Head circumference is smaller than normal (microcephaly) and affected males tend to be short. Small testes are also present after puberty.

There are some somatic manifestations present in most of the males with Sutherland-Haan syndrome. These include mild to moderate spastic diplegia (increased muscular tone with exaggeration of tendon reflexes of the legs), upslanting of the eye openings, brachycephaly (disproportionate shortness of the head), and a thin body build. Additionally, a few of the affected males may have anal abnormalities.

Mental impairment is mild to moderate with IQ ranging from 43 to 60. One male was reported to have an IQ in the 63-83 range (borderline).

Diagnosis

The diagnosis of Sutherland-Haan can only be made on the basis of the clinical findings in the presence of a family history consistent with X-linked inheritance of mental retardation and segregation of X chromosome markers in Xp11.2-Xq12. Unfortunately, there are no laboratory or radiographic changes that are specific for Sutherland-Haan syndrome.

Renpenning syndrome, another X-linked mental retardation syndrome, also has microcephaly, short stature, small testes, and upslanting of the eye openings. Furthermore, this syndrome is localized to Xp11.2-p11.4, which overlaps with the localization of Sutherland-Haan. However, males with Renpenning syndrome lack spasticity of the legs, brachycephaly, and a thin appearance. It is possible these two syndromes have different mutations in the same gene.

Chudley-Lowry syndrome also has microcephaly, short stature, and small testes. However, males have distinct facial features, similar to those of XLMR-hypotonic facies, and obesity. As with Renpenning syndrome, this syndrome may result from a different mutation in the same gene responsible for Sutherland-Haan syndrome.

Two other X-linked mental retardation syndromes (XLMR-hypotonic facies and X-linked hereditary bullous dystrophy) have microcephaly, short stature, and small testes. However, these conditions have different somatic features and are not localized to Xp11.2-Xq12.

Treatment and management

There is neither treatment nor cure available for Sutherland-Haan syndrome as of early 2001. Early educational intervention is advised for affected males. Some affected males may require living in a more controlled environment outside the home.

Prognosis

Life threatening concerns usually have not been associated with Sutherland-Haan syndrome. However, two affected males were found to have anal abnormalities, which required some form of surgery.

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Charles E. Schwartz, PhD

Swedish-type porphyria *see* **Porphyrias**

Systemic elastorrhexis *see* **Pseudoxanthoma elasticum**

Systemic sclerosis *see* **Scleroderma**

T

Talipes *see* **Clubfoot**

Tangier disease

Definition

Tangier disease is a rare autosomal recessive condition characterized by low levels of high density lipoprotein cholesterol (HDL-C) in the blood, accumulation of cholesterol in many organs of the body, and an increased risk of arteriosclerosis.

Description

Donald Fredrickson was the first to discover Tangier disease. He described this condition in 1961 in a five-year-old boy from Tangier Island who had large, yellow-orange colored tonsils that were engorged with cholesterol. Subsequent tests on this boy and his sister found that they both had virtually no high density lipoprotein cholesterol (HDL-C) in their blood stream. Other symptoms of Tangier disease such as an enlarged spleen and liver, eye abnormalities, and neurological abnormalities were later discovered in others affected with this disease.

It was not until 1999 that the **gene** for Tangier disease, called the ABCA1 gene, was discovered. This gene is responsible for producing a protein that is involved in the pathway by which HDL removes cholesterol from the cells of the body and transports it to the liver where it is digested and removed from the body.

Cholesterol is transported through the body as part of lipoproteins. Low density lipoproteins (LDL) and high density lipoproteins (HDL) are two of the major cholesterol transporting lipoproteins. Cholesterol attached to LDL (LDL-C) is often called "bad" cholesterol since it can remain in the blood stream for a long time, and high levels of LDL-C can increase the risk of clogging of the arteries (arteriosclerosis) and heart disease. Cholesterol attached to HDL is often called "good" cholesterol since it does not stay in the blood stream for a long period of time, and high levels are associated with a low risk of arteriosclerosis.

Research as of 2001 suggests that the ABCA1 protein helps to transport cholesterol found in the cell to the surface of the cell where it joins with a protein called ApoA-1 and forms an HDL-C complex. The HDL-C complex transports the cholesterol to the liver where the cholesterol is digested and removed from the body. This process normally prevents an excess accumulation of cholesterol in the cells of the body and can help to protect against arteriosclerosis.

Genetic profile

Changes in the ABCA1 gene, such as those found in Tangier disease, cause the gene to produce abnormal ABCA1 protein. The abnormal ABCA1 protein is less able to transport cholesterol to the surface of the cell, which results in an accumulation of cholesterol in the cell. The accumulation of cholesterol in the cells of the body causes most of the symptoms associated with Tangier disease. The decreased efficiency in removing cholesterol from the body can lead to an increased accumulation of cholesterol in the blood vessels, which can lead to a slightly increased risk of arteriosclerosis and ultimately an increased risk of heart attacks and strokes. The ABCA1 protein defect also results in decreased amounts of cholesterol available on the surface of the cell to bind to ApoA-1 and decreased cholesterol available to form HDL-C. This in turn results in the rapid degradation of ApoA-1 and reduced levels of ApoA-1 and HDL-C in the bloodstream. It also leads to lower levels of LDL-C in the blood.

The ABCA1 gene is found on chromosome 9. Since we inherit one chromosome 9 from our mother and one chromosome 9 from our father, we also

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Arteriosclerosis—Hardening of the arteries that often results in decreased ability of blood to flow smoothly.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Biochemical testing—Measuring the amount or activity of a particular enzyme or protein in a sample of blood, urine, or other tissue from the body.

Cholesterol—A fatty-like substance that is obtained from the diet and produced by the liver. Cells require cholesterol for their normal daily functions.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hemolytic anemia—Anemia that results from premature destruction and decreased numbers of red blood cells.

High density lipoprotein (HDL)—A cholesterol carrying substance that helps remove cholesterol from the cells of the body and deliver it to the liver where it is digested and removed from the body.

Low density lipoproteins (LDL)—A cholesterol carrying substance that can remain in the blood stream for a long period of time.

Lymph node—A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

Mucous membrane—Thin, mucous covered layer of tissue that lines organs such as the intestinal tract.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Spleen—Organ located in the upper abdominal cavity that filters out old red blood cells and helps fight bacterial infections. Responsible for breaking down spherocytes at a rapid rate.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.

Ureters—Tubes through which urine is transported from the kidneys to the bladder.

inherit two ABCA1 genes. People with Tangier disease have inherited one changed ABCA1 gene from their father and one changed ABCA1 gene from their mother, making Tangier disease an autosomal recessive condition.

Parents who have a child with Tangier disease are called carriers, since they each possess one changed ABCA1 gene and one unchanged ABCA1 gene. Carriers for Tangier disease do not have any of the symptoms associated with the disease, except for increased levels of HDL-C in their blood stream and a slightly increased risk of arteriosclerosis. The degree of risk of arteriosclerosis is unknown, and is dependent on other genetic and environmental factors, such as diet. Each child born to parents who are both carriers of Tangier disease has a 25% chance of having Tangier disease, a 50% chance of being a carrier, and a 25% chance of being neither a carrier nor affected with Tangier disease.

Demographics

Tangier disease is a very rare disorder with less than 100 cases diagnosed worldwide. Tangier disease affects both males and females.

Signs and symptoms

The symptoms of Tangier disease are quite variable but the most common symptoms of Tangier disease are enlarged, yellow-colored tonsils, an enlarged spleen, accumulation of cholesterol in the mucous membranes of the intestines, abnormalities in the nervous system (neuropathy), and an increased risk of arteriosclerosis. Less commonly seen symptoms are an enlarged liver, lymph nodes and thymus, and hemolytic anemia. Cholesterol accumulation has been seen in other organs such as the bone marrow, gall bladder, skin, kidneys, heart valves, ureters, testicles, and the cornea of the eye.

Symptoms involving the tonsils, intestines and spleen

The unusual appearance of the tonsils is due to an accumulation of cholesterol. Even when the tonsils are removed, small yellow patches at the back of the throat may be evident. The accumulation of cholesterol in the mucous membranes of the intestines results in the appearance of orange-brown spots on the rectum, and can occasionally result in intermittent diarrhea and abdominal pain. The enlargement of the spleen can result in anemia and decreased numbers of certain blood cells called platelets.

Nervous system abnormalities

Cholesterol can accumulate in the nerve cells which can result in nervous system abnormalities and symptoms such as loss of heat and pain sensation, weakness, increased sweating, burning prickling sensations, loss of feeling, eye muscle spasms, double vision, drooping eyelids, and decreased strength and reflexes. These symptoms can be mild to severe, and can be temporary or permanent. Most people with Tangier disease have some nervous system dysfunction, but in many cases the symptoms are mild and may be undetectable. Occasionally patients with Tangier disease experience progressive and debilitating nervous system abnormalities.

Arteriosclerosis

Since so few people are known to be affected with Tangier disease it is difficult to precisely predict their risk of developing arteriosclerosis and heart disease. Depending on their age, people with Tangier disease appear to have approximately four to six times increased risk for arteriosclerosis leading to heart disease. People over the age of 30 appear to have a six-fold increased risk. It is possible that Tangier patients are protected from higher risks of arteriosclerosis by lower than average levels of LDL-C in their blood stream.

Diagnosis

Tangier disease is diagnosed through assessment of clinical symptoms and biochemical testing. A diagnosis of Tangier disease should be considered in anyone with deposits of cholesterol on the cornea, an unexplained enlarged spleen or liver, or neurological abnormalities. Examination of the throat and tonsils and rectal mucous membrane should be performed on those suspected to have Tangier disease. Measurements of the total cholesterol, HDL-C, LDL-C, ApoA-1 and triglycerides should also be performed. Patients with Tangier disease have virtually no HDL-C in their bloodstream and ApoA-1 levels are reduced to one to three percent of normal. LDL-C levels are also reduced to approximately 40% of normal and triglyceride levels can be mildly elevated. As of 2001, DNA testing for Tangier disease is not available through clinical laboratories, although DNA testing on a clinical basis should be available in the future. Some laboratories may identify ABCA1 gene changes in patients as part of their research. Prenatal testing is only available if ABCA1 gene changes are identified in the parents.

Treatment and management

There is no treatment for Tangier disease and treatment of decreased HDL-C with medication is usually ineffective. Occasionally organs such as the spleen and tonsils are removed because of extensive accumulation of cholesterol. Arteriosclerosis may be treated through angioplasty or bypass surgery. Angioplasty involves inserting a small, hollow tube called a catheter with a deflated balloon through the groin or arm and into a clogged artery. The balloon is then inflated which enlarges the artery and compresses the blockage. Coronary artery disease can also be treated through bypass surgery, which is performed by taking a blood vessel from another part of the body and constructing an alternate path around the blocked part of the artery.

Prognosis

In most cases the prognosis for Tangier is disease is quite good. People who develop heart disease may, however, have a decreased lifespan depending on the severity of the disease and the quality of medical treatment.

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National Tay-Sachs and Allied Diseases Association. 2001 Beacon St., Suite 204, Brighton, MA 02135. (800) 906-8723. ntasd-Boston@worldnet.att.net. <http://www.ntsad.org>.

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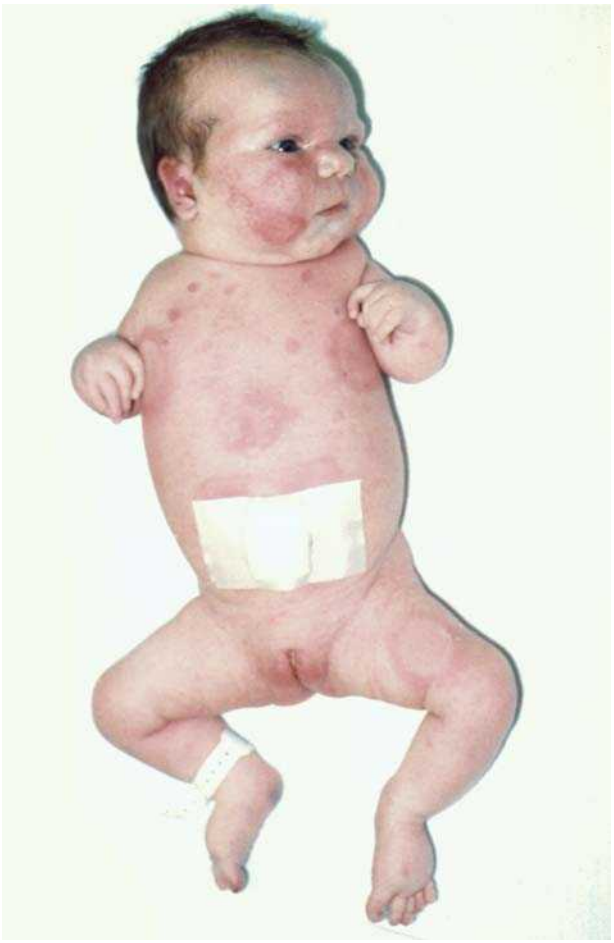
Lisa Maria Andres, MS, CGC

TAR syndrome

Definition

Thrombocytopenia-absent radius (TAR) syndrome is a rare condition that is apparent at birth. Affected infants are born with incomplete or missing forearms. Typically, the bone on the thumb side of the forearm (radius) is absent, but other bones may be missing or abnormally formed. TAR syndrome also causes life-threatening bleeding episodes due to low levels of platelets in the blood (thrombocytopenia). It is inherited in an autosomal recessive manner.



Absence of the radius bone (that found in the forearm) is a primary indication of TAR syndrome. This infant is missing both radius bones resuling in shortened arms. The bruising on the body results from thrombocytopenia, low blood platelet count, which impairs the blood clotting process. *(Greenwood Genetic Center)*

Description

Dr. S. Shaw first wrote about two siblings (a brother and a sister) with missing forearms and bleeding problems in 1956. Thirteen years later, Dr. Judith Hall gave the name and acronym of TAR syndrome to the disorder. She described three families containing nine individuals. TAR syndrome has also been called the tetraphocomelia-thrombocytopenia syndrome.

The forearm is comprised of two bones. The radius is the long bone on the thumb side of the forearm. The ulna is the long bone on the little finger side. In TAR syndrome, the radius is missing on each forearm. Many times the ulna may also be missing or shorter than normal.

As these bone deficiencies are quite obvious at birth, the forearms will look very short. In fact, the hand looks as if it comes directly from the elbow. In more severe cases, the bone of the upper arm is also missing, with the hand connected to the shoulder. Approximately 50% of the time there are other skeletal abnormalities, particularly in the lower limbs.

Each individual seems to be affected somewhat differently. For instance, some individuals with TAR syndrome might have one arm longer than the other arm; another might have both arms short, and bones missing in the feet; a third person might have all four limbs severely affected. The one constant feature is the absence of the radius bone. The forearm defects cause the hands to be bent inwards towards the body. However, the four fingers and thumb usually look normal.

The other main feature of the syndrome is thrombocytopenia. Thrombocytopenia means abnormally low levels of platelets in the blood. Platelets are made from cells called megakaryocytes. The megakaryocytes are

formed in the red bone marrow, lungs and spleen. In TAR syndrome, the megakaryoctyes are either absent, decreased in number or not formed properly. Therefore, the platelets are not properly made. The exact reason remains unknown.

When injury occurs, platelets are needed so that the blood can clot. The process is called blood coagulation. The platelets help initiate this process by attaching to the injured tissue, and clumping together, almost like a temporary patch. The platelets then release an enzyme called thromboplastin. Thromplastin acts to cleave a particle called fibrinogen (also in the blood) to fibrin. Fibrin is a hard substance that attaches to the injured area, and forms a meshwork (a blood clot). Along with other clotting factors, this permanently stops the bleeding.

In TAR syndrome, the normal process of making platelets is defective. The effect of this is excessive bleeding and bruising. These individuals have frequent nosebleeds and their skin bruises more easily. The platelet problem makes them more prone to bleeding inside the body, such as in the kidney or lungs. Bleeding can also occur inside the brain (intracranial hemorrhage), and be so severe that these infants die from the internal bleeding.

Genetic profile

There have been numerous instances of siblings, each with TAR syndrome. The parents were not affected. A few families have also been seen where the parents were said to be closely related (i.e. may have shared the same altered **gene** within the family). For these reasons, TAR syndrome is most likely an autosomal recessive disorder. Autosomal means that both males and females can have the condition. Recessive means that both parents would be carriers of a single copy of the responsible gene. Autosomal recessive disorders occur when a person inherits a particular pair of genes which do not work correctly. The chance that this would happen to children of carrier parents is 25% (1 in 4) for each pregnancy.

It is known that the limbs (arms, legs), the heart and the precursors of the blood system form between the fourth and eighth week of pregnancy. The birth defects seen in TAR syndrome must occur during this crucial period of development. As of 2001, the genetic cause remains unknown.

Demographics

TAR syndrome affects both males and females equally. It most likely occurs in every racial and ethnic group. It is estimated that one in every 250,000 infants are born with TAR syndrome. In all, more than 200 individuals with this disorder have been described in the medical literature.

KEY TERMS

Cordocentesis—A prenatal diagnostic test, usually done between 16-30 weeks of gestation. Using ultrasound guidance, a thin needle is introduced through the abdomen into the amniotic sac. A blood sample is taken directly from the umbilical cord. Tests can then be done on the blood sample.

Intracranial hemorrhage—Abnormal bleeding within the space of the skull and brain.

Tetralogy of Fallot—A congenital heart defect consisting of four (tetralogy) associated abnormalities: ventricular septal defect (VSD—hole in the wall separating the right and left ventricles); pulmonic stenosis (obstructed blood flow to the lungs); the aorta "overrides" the ventricular septal defect; and thickening (hypertrophy) of the right ventricle.

Tetraphocomelia—Absence of all, or a portion of, all four limbs. The hands or feet may be attached directly to the trunk.

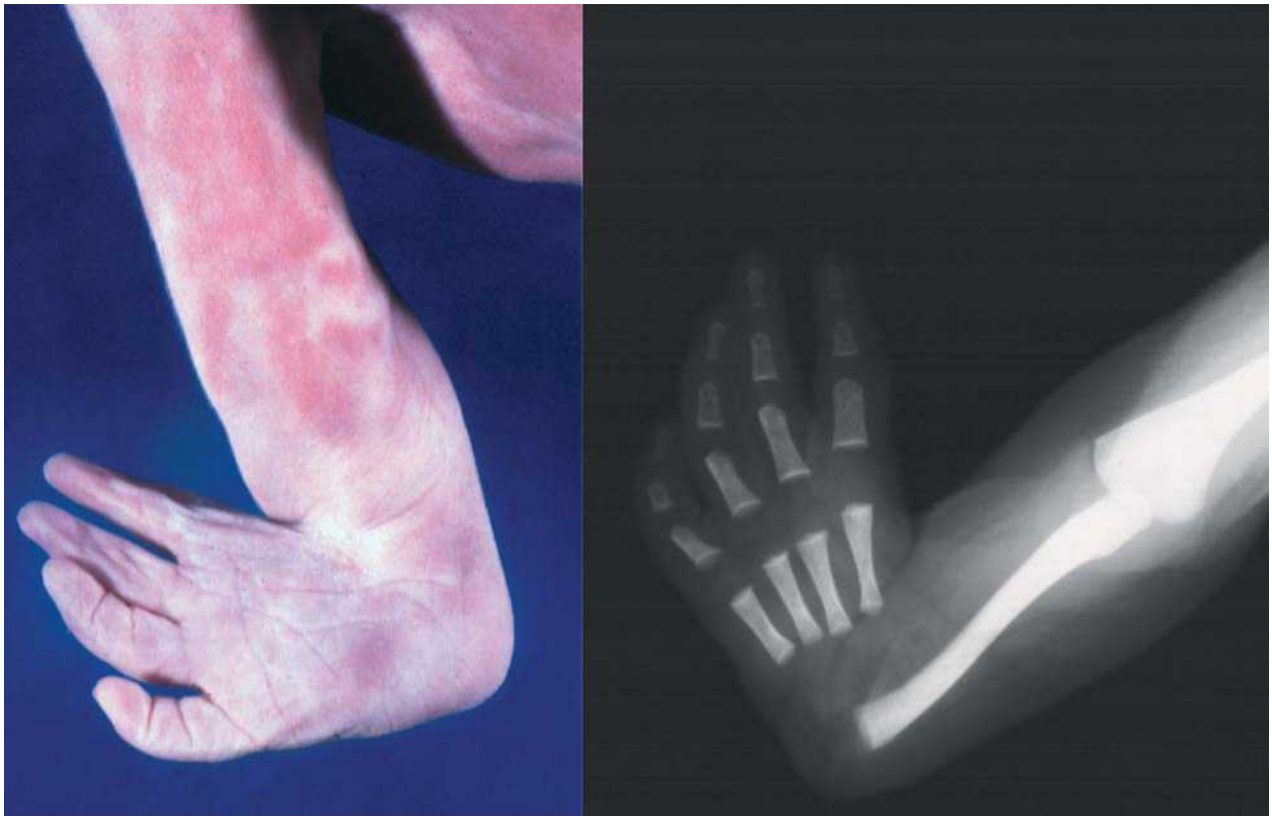
Thalidomide—A mild sedative that is teratogenic, causing limb, neurologic, and other birth defects in infants exposed during pregnancy. Women used thalidomide (early in pregnancy) in Europe and in other countries between 1957 and 1961. It is still available in many places, including the United States, for specific medical uses (leprosy, AIDS, cancer).

Signs and symptoms

Aside from the limb deficiencies and the thrombocytopenia, the heart can also be affected. Around one-third of these infants are born with heart defects. These are usually found at birth. The heart problems include holes in the atrial chamber of the heart (atrial septal defect) and tetralogy of Fallot. The name tetralogy of Fallot means there are four different defects of the heart. Because of the high risk for excessive bleeding to occur, these infants are not good candidates for heart surgery. Some of them have died from heart failure.

Diagnosis

Diagnosis of TAR syndrome is made with the use of x ray of the bones and by testing for low platelet levels in



The forearm abnormalities in patients with TAR syndrome cause the hands to be bent inwards towards the body. The arm x ray shown here is missing the radius bone as well as the thumb. *(Greenwood Genetic Center)*

the blood at birth. TAR syndrome can be diagnosed during pregnancy. By using ultrasound (sound waves) at around 16-20 weeks of pregnancy, the shortening of the arms can be seen. A second test is then done called cordocentesis. In this procedure, using ultrasound guidance, a thin needle is introduced through the mother's abdomen into the amniotic sac. A blood sample is taken directly from the umbilical cord. With this blood sample, a count of the platelets can be done. If the platelet count is low, along with the short arms (absent radii), the diagnosis of TAR syndrome is made.

Prognosis

About 40% of these individuals die in infancy, usually due to severe bleeding episodes. Cow's milk allergy or intolerance is a common problem. Stomach infections seem particularly threatening to these infants, and can also trigger the bleeding episodes. The thrombocytopenia is treated with platelet transfusions, which may or may not control the bleeding, and death may occur.

The thrombocytopenia seen in TAR syndrome does improve with age. If these individuals survive the first two years of life, they appear to have a normal life span. However, the easy bruising continues throughout life. Many females with TAR syndrome also have abnormal menstrual periods, possibly related to the thrombocytopenia.

Surgery is sometimes done in an attempt to straighten and improve the use of their hands. They may wear corrective braces for the forearms. Many of these individuals develop arthritis, especially of the wrists and knees as they get older. This may further limit the use of their hands and legs. However, most individuals with TAR syndrome learn to adapt well to their disability, and lead productive lives.

Resources

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ORGANIZATIONS

T.A.R.S.A. Thrombocytopenia Abset Radius Syndrome Association. 212 Sherwood Drive, Linwood, NJ 08324-7658. (609) 927-0418.

WEBSITES

The Association for Children with Hand or Arm Deficiency. <http://www.reach.org.uk.htm>.

Kevin M. Sweet, MS, CGC

KEY TERMS

Ganglioside—A fatty (lipid) substance found within the brain and nerve cells.

Tay-Sachs disease

Definition

Tay-Sachs disease is a genetic disorder caused by a missing enzyme that results in the accumulation of a fatty substance in the nervous system. This results in disability and death.

Description

Gangliosides are a fatty substance necessary for the proper development of the brain and nerve cells (nervous system). Under normal conditions, gangliosides are continuously broken down, so that an appropriate balance is maintained. In Tay-Sachs disease, the enzyme necessary for removing excess gangliosides is missing. This allows gangliosides to accumulate throughout the brain, and is responsible for the disability associated with the disease.

Demographics

Tay-Sachs disease is particularly common among Jewish people of Eastern European and Russian (Ashkenazi) origin. About one out of every 3,600 babies born to Ashkenazi Jewish couples will have the disease. Tay-Sachs is also more common among certain French-Canadian and Cajun French families.

Genetic profile

Tay-Sachs is caused by a defective **gene**. Genes are located on **chromosomes**, and serve to direct specific development/processes within the body. The genetic defect in Tay-Sachs disease results in the lack of an enzyme called hexosaminidase A. Without this enzyme, gangliosides cannot be degraded. They build up within the brain, interfering with nerve functioning. Because it is a recessive disorder, only people who receive two defective genes (one from the mother and one from the father) will actually have the disease. People who have only one defective gene and one normal gene are called carriers. They carry the defective gene and thus the possibility of passing the gene and/or the disease onto their offspring.

When a carrier and a non-carrier have children, none of their children will actually have Tay-Sachs. It is likely that 50% of their children will be carriers themselves. When two carriers have children, their children have a 25% chance of having normal genes, a 50% chance of being carriers of the defective gene, and a 25% chance of having two defective genes. The two defective genes cause the disease itself.

Signs and symptoms

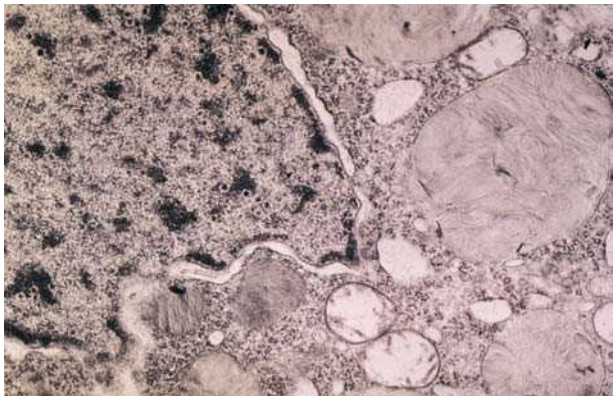
Classic Tay-Sachs disease strikes infants around the age of six months. Up until this age, the baby will appear to be developing normally. When Tay-Sachs begins to show itself, the baby will stop interacting with other people, and develop a staring gaze. Normal levels of noise will startle the baby to an abnormal degree. By about one year of age, the baby will have very weak, floppy muscles, and may be completely blind. The head will be quite large. Patients also present with loss of peripheral (side) vision, inability to breathe and swallow, and paralysis as the disorder progresses. Seizures become a problem between ages one and two, and the baby usually dies by about age four.

A few variations from this classical progression of Tay-Sachs disease are possible:

- Juvenile hexosaminidase A deficiency. Symptoms appear between ages two and five; the disease progresses more slowly, with death by about 15 years of age.
- Chronic hexosaminidase A deficiency. Symptoms may begin around age five, or may not occur until age 20-30. The disease is milder. Speech becomes slurred. The individual may have difficulty walking due to weakness, muscle cramps, and decreased coordination of movements. Some individuals develop mental illness. Many have changes in intellect, hearing, or vision.

Diagnosis

Examination of the eyes of a child with Tay-Sachs disease will reveal a very characteristic cherry-red spot at the back of the eye (in an area called the retina). Tests to determine the presence and quantity of hexosaminidase A can be performed on the blood, specially treated skin cells, or white blood cells. A carrier will have about half



Section of brain tissue from patient with Tay-Sachs disease. *(Custom Medical Stock Photo, Inc.)*

of the normal level of hexosaminidase A present, while a patient with the disease will have none.

Treatment

There is no treatment for Tay-Sachs disease.

Prognosis

A child with classic Tay-Sachs disease rarely survives past age four. Because the chronic form of Tay-Sachs has been discovered recently, prognosis for this type of the disease is not completely known.

Prevention

Prevention involves identifying carriers of the disease and providing them with appropriate information concerning the chance of their offspring having Tay-Sachs disease. When the levels of hexosaminidase A are half the normal level a person is a carrier of the defective gene. Blood tests of carriers reveals reduction of hexosaminidase A.

When a woman is already pregnant, tests can be performed on either the cells of the baby (aminocentesis) or the placenta (chorionic villus sampling) to determine whether the baby will have Tay-Sachs disease.

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ORGANIZATIONS

Late Onset Tay-Sachs Foundation. 1303 Paper Mill Road, Erdenheim, PA 19038. (800) 672-2022.

March of Dimes Birth Defects Foundation. National Office. 1275 Mamaroneck Avenue, White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Tay-Sachs and Allied Diseases Association, Inc. 2001 Beacon Street, Suite 204, Brighton, MA 02146. (800) 906-8723. Fax: 617-277-0134. NTSAD-Boston@worldnet.att.net. <http://www.ntsad.org>.

Laith Farid Gulli, MD

Teratogen

Definition

A teratogen is any environmental influence that adversely affects the normal development of the fetus.

Description

Abnormal fetal development may result from exposure to a teratogen. There are four different teratogen categories: physical agents (radiation and hyperthermia), metabolic conditions affecting the mother, infection, and drugs (like thalidomide) and alcohol.

Physical agents

Hyperthermia

Women whose body temperature is raised while pregnant may have abnormalities result in their fetus. The rise in body temperature can be caused by infection or by spending time in hot areas such as a sauna or hot tub.

Ionizing radiation–mutagens versus teratogens

Any outside agent (like radiation) interfering with the process of development is considered a teratogen. Development is the process in which a tiny mass of undifferentiated cells (the embryo) multiplies and differentiates into the kidney, liver, heart, bone, muscles, and so on. Mutagens, however, are agents that directly affect and disrupt **DNA**, the genetic blueprint of an organism. Some agents, like radiation, are mutagens and teratogens.

Ionizing radiation can cause defects either in development or it can damage DNA directly.

Metabolic disease

Infants of women with metabolic disorders have increased risks for abnormalities. Diabetic women, for example, are three to four times more likely to have fetuses with congenital abnormalities than infants of mothers without diabetes. The metabolic disease of the mother can have genetic or other causes.

Infection

There are a number of known infectious organisms which are teratogenic to the fetus, some of which cause damage directly, and some of which damage the fetus by causing a fever and raising the temperature of the mother.

Alcohol and drugs

Thalidomide

A dramatic example of a teratogen is thalidomide. In the early 1960s it was shown that more than 7,000 women who took the anti-nausea drug thalidomide during their pregnancy had children with very short or absent arms and legs. Other abnormalities were also seen in the children, such as the absence of ears, as well as heart and intestinal malformations. Affected infants were born to women who took thalidomide during the critical time period, also known as the period of susceptibility.

Period of susceptibility: The example of Thalidomide

Thalidomide also teaches the importance of timing in the action of teratogens. Only a small amount of thalidomide was necessary to cause birth defects, but it had to be taken between 34 and 50 days after conception in order to harm the embryo. The time when teratogens can act, in this case from day 34 to day 50 after conception, is called the period of susceptibility. Since organ development in the unborn child occurs at different times, it was shown that taking thalidomide on different days caused the infants to have a variety of defects (heart vs. ears vs. limb formation). Drugs very often affect specific parts of the process of development. Before, or after, the processes take place, the drug will have no effect. Of course many teratogens, like thalidomide, work on a number of different developmental processes at different times (sometimes they are consecutive times, or they may be non-consecutive: for example from days 16 to 20 and days 24 to 48). The period of susceptibility of the child to most teratogens is between the third and eighth week after conception.

KEY TERMS

Development—The process whereby undifferentiated embryonic cells replicate and differentiate into limbs, organ systems, and other body components of the fetus.

Maternal—Relating to the mother.

Mutagen—An environmental influence that causes changes in DNA.

Period of susceptibility—The time when teratogens can cause harm to the developing fetus.

Dose and duration: The example of alcohol

The most common teratogen, alcohol, illustrates the important concept that the dose of a teratogen (for example, the number of alcoholic drinks a mother has) and duration of exposure to a teratogen (for example, the number of days a mother drinks alcohol) both play an important role in the effect of a teratogen. Alcohol can have a wide range of effects on a fetus, from no mental change or very mild mental changes (usually a small dose of alcohol) to full-blown **fetal alcohol syndrome**, in which the infant is severely retarded. Even two glasses of alcohol can be teratogenic to a fetus, but the mental retardation and characteristic facial changes seen in full-blown fetal alcohol syndrome generally requires the mother to drink 2-3 oz of alcohol per day for a sustained period of time (the exact amount of time is not known) during pregnancy. Thus, dose and duration help determine the severity of a teratogen's effects.

Other factors that affect teratogens

Although the dose and duration are important in determining how much of an effect alcohol will have on the fetus, other factors have an impact, too. When normal mice and mutant mice are given the same dose of a particular teratogen, the mutant mice are affected much more severely. This means that in humans, the genetic makeup of the fetus helps determine to what extent the teratogen will affect the fetus. A baby with one particular set of genes might be severely affected by the mother drinking one glass of alcohol, while another fetus may be unaffected by the first or even second glass of alcohol. The outcome of teratogens probably depends on a combination of factors: the mother's condition (genetic or

otherwise), the genetic background of the fetus, and the dose and duration of the teratogen. However, the importance of each factor probably varies greatly from teratogen to teratogen and from individual to individual.

Although the discussion of these teratogenic concepts has revolved around examples from the category of drugs and alcohol, the concepts may be applied to any of the categories of teratogens.

Demographics

Exact numbers of infants affected by teratogens are difficult to estimate. *Langman's Medical Embryology* states 4-6% of all infants will have major developmental or genetic abnormalities. This source estimates that of the children with major abnormalities, 10% can be attributed to teratogens, 20-25% can be attributed to genetic and environmental influences, and 40-60% of the abnormalities are due to unknown causes (possibly teratogenic). That means as many as 95% of all major birth disorders may involve teratogens.

Diagnosis

The diagnosis varies from teratogen to teratogen. Some genetic diseases and teratogens can present with the same abnormalities and symptoms. If the **gene** causing the disorder has been isolated and is well understood, the difference between a genetic and a teratogenic disorder may be established. Many abnormalities in children go unexplained. In these cases, teratogen exposure should be considered.

Treatment, prevention, and the period of susceptibility

Treatment options and how well they work vary widely according to the teratogen. The best course is to prevent teratogen exposure, or reduce the exposure as much as possible. Prevention is complicated because very often women may not realize they are pregnant until the middle of the period of susceptibility. Substances that are not harmful to an adult, like the derivatives of retinoic acid found in a number of skin creams, alcohol, and many prescription drugs, can be extremely harmful to the fetus. Retinoic acid, for example, has a period of susceptibility from days 20-35 after conception—a time when many women might not realize they are pregnant.

Thus, women who are engaging in activities that can lead to pregnancy and want to avoid any potential damage to their fetus should attempt to avoid teratogenic substances (including a large number of over-the-counter, prescription, and illegal drugs). Alternatively, women can also prevent most damage to the fetus by closely monitoring their pregnancy status and avoiding teratogens as soon as pregnancy occurs.

Partial list of teratogens

Drugs and chemicals

- Alcohol
- Aminoglycosides
- Aminopterin
- Antithyroid agents
- Bromine
- Cortisone
- Diethylstilbesterol (DES)
- Diphenylhydantoin
- Heroin
- Lead
- Methylmercury
- Penicillamine
- Retinoic acid (Isoretinoin, Accutane)
- Tetracycline
- Thalidomide
- Trimethadione
- Valproic acid
- Warfarin

Physical agents

- Hyperthermia (fever, sauna)
- Ionizing radiation (x rays)

Infectious organisms

- Coxsackie virus
- Cytomegalovirus
- Herpes simplex virus
- Parvovirus
- Rubella
- Toxoplasma gondii
- Treponema pallidum (syphilis)

Metabolic conditions in the mother

- Autoimmune disease
- Diabetes
- Malnutrition
- Phenylketonuria

Resources

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WEBSITES

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Michael V. Zuck, PhD

Testicular feminization syndrome *see* **Androgen insensitivity syndrome**

Thalassemia

Definition

Thalassemia describes a group of inherited disorders characterized by reduced or absent amounts of hemoglobin, the oxygen-carrying protein inside the red blood cells. There are two basic groups of thalassemia disorders: alpha thalassemia and beta thalassemia. These conditions cause varying degrees of anemia, which can range from insignificant to life threatening.

Description

All types of thalassemias are considered quantitative diseases of hemoglobin, because the quantity of hemoglobin produced is reduced or absent. Usual adult hemoglobin is made up of three components: alpha globin, beta globin, and heme. Thalassemias are classified according to the globin that is affected, hence the names *alpha* and *beta* thalassemia. Although both classes of thalassemia affect the same protein, the alpha and beta thalassemias are distinct diseases that affect the body in different ways.

Beta thalassemia

Beta thalassemia may be the most well-known type of thalassemia and is also called Cooley's anemia. It is caused by a change in the **gene** for the beta globin component of hemoglobin. Beta thalassemia causes variable anemia that can range from moderate to severe, depending in part on the exact genetic change underlying the disease. Beta thalassemia can be classified based on clinical symptoms. *Beta thalassemia major* usually causes severe anemia that can occur within months after birth. If left untreated, severe anemia can result in insufficient growth and development, as well as other characteristic physical complications that can lead to a dramatically decreased life expectancy. Fortunately, in developed countries, beta thalassemia is usually identified by screening in the newborn period, before symptoms have developed. Children who are identified early can be started on ongoing blood transfusion therapy as needed. Although transfusion therapy prevents many of the complications of severe anemia, the body is unable to eliminate the excess iron contained in the transfused blood. Over time, this excess iron deposits in tissues and organs, resulting in damage and organ failure. Another medication must be administered to help the body eliminate the excess iron and prevent iron-overload complications. *Beta thalassemia intermedia* describes the disease in individuals who have moderate anemia that only requires blood transfusions intermittently, if at all.

Alpha thalassemia

Alpha thalassemia is the result of changes in the genes for the alpha globin component of hemoglobin. There are two main types of alpha thalassemia disease: hemoglobin H disease and alpha thalassemia major. The two diseases are quite different from beta thalassemia, as well as from one another. Individuals with hemoglobin H disease can experience events of hemolytic anemia—anemia caused by the rapid breakdown of the red blood cells. These events are thought to be triggered by various environmental causes, such as infection and/or exposure to certain chemicals. Hemoglobin H disease is in most cases more mild than beta thalassemia. It does not generally require transfusion therapy. *Alpha thalassemia major* is a very serious disease that results in severe anemia that begins even before birth. Most affected babies do not survive to be born or die shortly after birth.

Demographics

The thalassemias are among the most common genetic diseases worldwide. Both alpha and beta thalassemia have been described in individuals of almost every ancestry, but the conditions are more common among certain ethnic groups. Unaffected carriers of all

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bilirubin—A yellow pigment that is the end result of hemoglobin breakdown. This pigment is metabolized in the liver and excreted from the body through the bile. Bloodstream levels are normally low; however, extensive red cell destruction leads to excessive bilirubin formation and jaundice.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Bone marrow transplantation—A medical procedure used to treat some diseases that arise from defective blood cell formation in the bone marrow. Healthy bone marrow is extracted from a donor to replace the marrow in an ailing individual. Proteins on the surface of bone marrow cells must be identical or very closely matched between a donor and the recipient.

Desferoxamine—The primary drug used in iron chelation therapy. It aids in counteracting the life-threatening buildup of iron in the body associated with long-term blood transfusions.

Globin—One of the component protein molecules found in hemoglobin. Normal adult hemoglobin has a pair each of alpha-globin and beta-globin molecules.

Heme—The iron-containing molecule in hemoglobin that serves as the site for oxygen binding.

Hemoglobin—Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hemoglobin A—Normal adult hemoglobin that contains a heme molecule, two alpha-globin molecules, and two beta-globin molecules.

Hemoglobin electrophoresis—A laboratory test that separates molecules based on their size, shape, or electrical charge.

Hepatomegaly—An abnormally large liver.

HLA type—Refers to the unique set of proteins called human leukocyte antigens. These proteins are present on each individual's cells and allow the immune system to recognize 'self' from 'foreign'. HLA type is particularly important in organ and tissue transplantation.

Hydroxyurea—A drug that has been shown to induce production of fetal hemoglobin. Fetal hemoglobin has a pair of gamma-globin molecules in place of the typical beta-globins of adult hemoglobin. Higher-than-normal levels of fetal hemoglobin can ameliorate some of the symptoms of thalassemia.

Iron overload—A side effect of frequent blood transfusions in which the body accumulates abnormally high levels of iron. Iron deposits can form in organs, particularly the heart, and cause life-threatening damage.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Red blood cell—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

Screening—Process through which carriers of a trait may be identified within a population.

Splenomegaly—Enlargement of the spleen.

types of thalassemia traits do not experience health problems. In fact, thalassemia trait is protective against malaria, a disease caused by blood-borne parasites transmitted through mosquito bites. According to a widely accepted theory, most genetic changes—mutations—that cause thalassemia occurred multiple generations ago. Coincidentally, these mutations increased the likelihood that carriers would survive malaria infection. Survivors passed the mutation onto their offspring, and the trait became established throughout areas where malaria is common. As populations migrated, so did the thalassemia traits.

Beta thalassemia trait is seen most commonly in people with the following ancestry: Mediterranean (including North African, and particularly Italian and Greek), Middle Eastern, Indian, African, Chinese, and Southeast Asian (including Vietnamese, Laotian, Thai, Singaporean, Filipino, Cambodian, Malaysian, Burmese, and Indonesian). Alpha thalassemia trait is seen with increased frequency in the same ethnic groups. However, there are different types of alpha thalassemia traits within these populations. The frequency of hemoglobin H disease and alpha thalassemia major depends on the type of alpha thalassemia trait. The populations in which alpha thalassemia diseases are most common include Southeast Asians and Chinese (particularly Southern Chinese).

It is difficult to obtain accurate prevalence figures for various types of thalassemia within different populations. This difficulty arises due to testing limitations in determining exact genetic diagnoses, as well as the fact that many studies have focused on small, biased hospital populations.

Two studies reflect prevalence figures that can be helpful in counseling families and determining who to screen for beta thalassemia. Between the years of 1990 and 1996, the State of California screened over 3.1 million infants born in this multiethnic state for beta thalassemia. Approximately 1 in 114,000 infants had beta thalassemia major, with prevalence rates being highest among Asian Indians (about 1 in 4,000), Southeast Asians (about 1 in 10,000), and Middle Easterners (about 1 in 7,000). Another type of beta thalassemia disease, E/beta thalassemia, was represented in approximately 1 in 110,000 births, all of which being of Southeast Asian ancestry. Among Southeast Asians, the prevalence of E/beta thalassemia was approximately 1 in 2,600 births. This is in keeping with the observation that hemoglobin E trait carrier rates are relatively high within the Southeast Asian population: 16% in a study of 768 immigrants to California, and up to 25% in some specific Southeast Asian populations such as Cambodians. While these California studies address some of the limitations of earlier population studies, the pattern observed in California is expected to be different in other areas of the United States and the world. For example, Italians are underrepresented in this population when compared to the East Coast of the United States.

Determining prevalence figures for alpha thalassemia is even more difficult due to increased limitations in diagnostic testing. All types of alpha thalassemia disease are most common among people of Southeast Asian and Chinese descent, for reasons that become clearer with an understanding of the underlying genetics of alpha thalassemia. One study of 500 pregnant women in Northern Thailand estimated a frequency of 1 in 500 pregnancies affected by alpha thalassemia major, for example. Prevalence of alpha thalassemia disease is significantly lower in the United States owing primarily to immigration patterns. However at least one state, California, has observed growing hemoglobin H disease incidence rates that are high enough to justify universal newborn screening for the condition.

Genetic profile

Humans normally make several types of the oxygen-carrying protein hemoglobin. An individual's stage in development determines whether he or she makes primarily embryonic, fetal, or adult hemoglobins. All types of hemoglobin are made of three components: heme, alpha (or alpha-like) globin, and beta (or beta-like) globin. All types of thalassemia are caused by changes in either the alpha- or beta-globin gene. These changes cause little or no globin to be produced. The thalassemias are, therefore, considered quantitative hemoglobin diseases. All types of thalassemias are recessively inherited, meaning that a genetic change must be inherited from both the mother and the father. The severity of the disease is influenced by the exact thalassemia mutations inherited, as well as other genetic and environmental factors. There are rare exceptions, notably with beta thalassemia, where globin gene mutations exhibit a dominant pattern of **inheritance** in which only one gene needs to be altered in order to see disease expression.

Beta thalassemia

Most individuals have two normal copies of the beta globin gene, which is located on chromosome 11 and makes the beta globin component of normal adult hemoglobin, hemoglobin A. There are approximately 100 genetic mutations that have been described that cause beta thalassemia, designated as either beta0 or beta+ mutations. No beta globin is produced with a beta0 mutation, and only a small fraction of the normal amount of beta globin is produced with a beta+ mutation.

When an individual has one normal beta globin gene and one with a beta thalassemia mutation, he or she is said to carry the beta thalassemia trait. Beta thalassemia trait, like other hemoglobin traits, is protective against malaria infection. Trait status is generally thought not to cause health problems, although some women with beta thalassemia trait may have an increased tendency toward anemia during pregnancy.

When two members of a couple carry the beta thalassemia trait, there is a 25% chance that each of their children will inherit beta thalassemia disease by inheriting two beta thalassemia mutations, one from each parent. The clinical severity of the beta thalassemia

disease—whether an individual has beta thalassemia intermedia or beta thalassemia major—will depend largely on whether the mutations inherited are beta0 thalassemia or beta+ thalassemia mutations. Two beta0 mutations generally lead to beta thalassemia major, and two beta+ thalassemia mutations generally lead to beta thalassemia intermedia. Inheritance of one beta0 and one beta+ thalassemia mutation tends to be less predictable.

Although relatively uncommon, there are other thalassemia-like mutations that can affect the beta globin gene. Hemoglobin E is the result of a substitution of a single nucleotide. This change results in a structurally altered hemoglobin that is produced in decreased amounts. Therefore, hemoglobin E is unique in that it is both a quantitative (i.e. thalassemia-like) and qualitative trait. When co-inherited with a beta thalassemia trait, it causes a disease that is almost indistinguishable from beta thalassemia disease. Large deletions around and including the beta globin gene can lead to delta/beta thalassemia or hereditary persistence of fetal hemoglobin (HPFH). Interestingly, delta/beta thalassemia trait behaves very similarly to beta thalassemia trait clinically. However, HPFH trait does not tend to cause hemoglobin disease when co-inherited with a second thalassemia or other beta globin mutation.

Alpha thalassemia

Most individuals have four normal copies of the alpha globin gene, two copies on each chromosome 16. These genes make the alpha globin component of normal adult hemoglobin, which is called hemoglobin A. Alpha globin is also a component of fetal hemoglobin and the other major adult hemoglobin called hemoglobin A2. Mutations of the alpha globin genes are usually deletions of the gene, resulting in absent production of alpha globin. Since there are four genes (instead of the usual two) to consider when looking at alpha globin gene inheritance, there are several alpha globin types that are possible.

Absence of one alpha globin gene leads to a condition known as silent alpha thalassemia trait. This condition causes no health problems and can be detected only by special **genetic testing**. Alpha thalassemia trait occurs when two alpha globin genes are missing. This can occur in two ways. The genes may be deleted from the same chromosome, causing the 'cis' type of alpha thalassemia trait. Alternately, they may be deleted from different **chromosomes**, causing the 'trans' type of alpha thalassemia trait. In both instances, there are no associated health problems, although the trait status may be detected by more routine blood screening.

Hemoglobin H disease results from the deletion of three alpha globin genes, such that there is only one functioning gene. Typically, this can occur when one parent carries the silent alpha thalassemia trait, and the other parent carries the 'cis' type of the alpha thalassemia trait. In this situation, there is a 25% chance for hemoglobin H disease in each of such a couple's children.

Hemoglobin H disease-like symptoms can also be a part of a unique condition called alpha thalassemia mental retardation syndrome. Alpha thalassemia mental retardation syndrome can be caused by a deletion of a significant amount of chromosome 16, affecting the alpha globin genes. This is usually not inherited, but rather occurs sporadically in the affected individual. Affected individuals have mild hemoglobin H disease, mild-to-moderate mental retardation, and characteristic facial features. This syndrome can also occur as a sex-linked form in which a mutation is inherited in a particular gene on the X chromosome. This gene influences alpha globin production, as well as various other developmental processes. Individuals affected with this form of the syndrome tend to have more severe mental retardation, delayed development, nearly absent speech, characteristic facial features, and genital-urinary abnormalities.

Alpha thalassemia major results from the deletion of all four alpha globin genes, such that there are no functioning alpha globin genes. This can occur when both parents carry the 'cis' type of the alpha thalassemia trait. In this situation, there is a 25% chance for alpha thalassemia major in each of such a couple's children.

Diagnosis

Thalassemia may be suspected if an individual shows signs that are suggestive of the disease. In all cases, however, laboratory diagnosis is essential to confirm the exact diagnosis and to allow for the provision of accurate **genetic counseling** about recurrence risks and testing options for parents and affected individuals. Screening is likewise recommended to determine trait status for individuals of high-risk ethnic groups.

The following tests are used to screen for thalassemia disease and/or trait:

- Complete blood count
- Hemoglobin electrophoresis with quantitative hemoglobin A2 and hemoglobin F
- Free erythrocyte-protoporphyrin (or ferritin or other studies of serum iron levels)

A complete blood count will identify low levels of hemoglobin, small red blood cells, and other red blood

cell abnormalities that are characteristic of a thalassemia diagnosis. Since thalassemia trait can sometimes be difficult to distinguish from iron deficiency, tests to evaluate iron levels are important. A hemoglobin electrophoresis is a test that can help identify the types and quantities of hemoglobin made by an individual. This test uses an electric field applied across a slab of gel-like material. Hemoglobins migrate through this gel at various rates and to specific locations, depending on their size, shape, and electrical charge. Isoelectric focusing and high-performance liquid chromatography (HPLC) use similar principles to separate hemoglobins and can be used instead of or in various combinations with hemoglobin electrophoresis to determine the types and quantities of hemoglobin present. Hemoglobin electrophoresis results are usually within the normal range for all types of alpha thalassemia. However, hemoglobin A2 levels and sometimes hemoglobin F levels are elevated when beta thalassemia disease or trait is present. Hemoglobin electrophoresis can also detect structurally abnormal hemoglobins that may be co-inherited with a thalassemia trait to cause thalassemia disease (i.e. hemoglobin E) or other types of hemoglobin disease (i.e. sickle hemoglobin). Sometimes DNA testing is needed in addition to the above screening tests. This can be performed to help confirm the diagnosis and establish the exact genetic type of thalassemia.

Diagnosis of thalassemia can occur under various circumstances and at various ages. Several states offer thalassemia screening as part of the usual battery of blood tests done for newborns. This allows for early identification and treatment. Thalassemia can be identified before birth through the use of prenatal diagnosis. Chorionic villus sampling (CVS) can be offered as early as 10 weeks of pregnancy and involves removing a sample of the placenta made by the baby and testing the cells. **Amniocentesis** is generally offered between 15 and 22 weeks of pregnancy, but can sometimes be offered earlier. Two to three tablespoons of the fluid surrounding the baby is removed. This fluid contains fetal cells that can be tested. Pregnant woman and couples may choose prenatal testing in order to prepare for the birth of a baby that may have thalassemia. Alternately, knowing the diagnosis during pregnancy allows for the option of pregnancy termination. Preimplantation genetic diagnosis (PGD) is a relatively new technique that involves in-vitro fertilization followed by genetic testing of one cell from each developing embryo. Only the embryos unaffected by sickle cell disease are transferred back into the uterus. PGD is currently available on a research basis only and is relatively expensive.

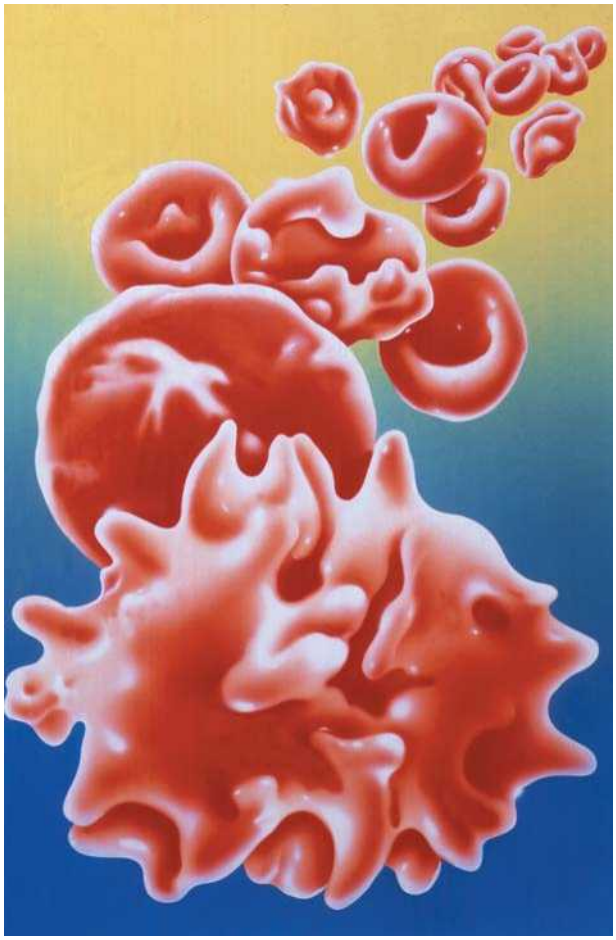
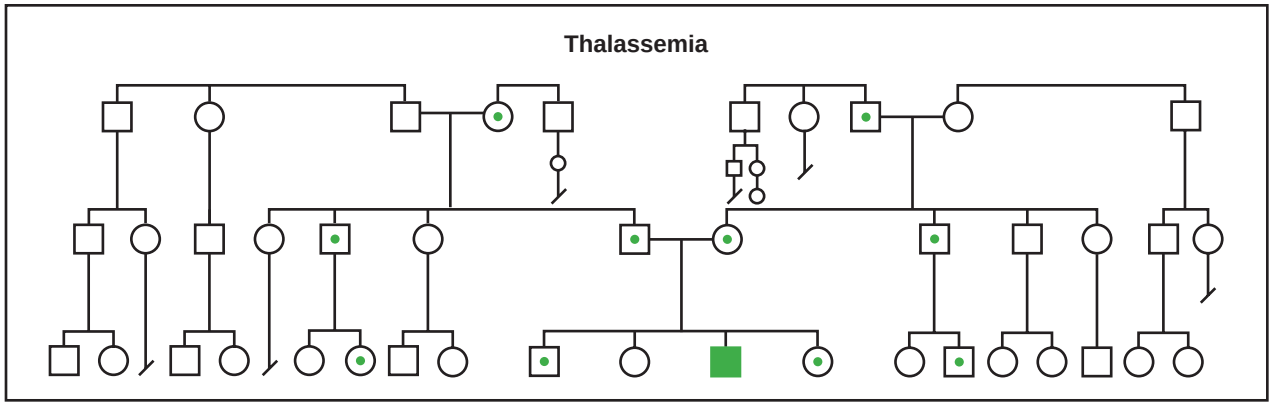


Illustration depicting the various abnormal red blood cells of thalassemia. The red blood cells rapidly break up as they move through the body due to poor hemoglobin production. *(Photo Researchers, Inc.)*

Signs and symptoms

Beta thalassemia

Beta thalassemia major is characterized by severe anemia that can begin months after birth. In the United States and other developed countries beta thalassemia is identified and treated early and effectively. Therefore, the following discussion of symptoms applies primarily to affected individuals in the past and unfortunately in some underdeveloped countries now. If untreated, beta thalassemia major can lead to severe lethargy, paleness, and growth and developmental delay. The body attempts to compensate by producing more blood, which is made inside the bones in the marrow. However, this is ineffective without the needed genetic instructions to make enough functioning hemoglobin. Instead, obvious bone expansion and changes occur that cause characteristic facial and other changes in appearance, as well as



(Gale Group)

increased risk of fractures. Severe anemia taxes other organs in the body—such as the heart, spleen, and liver—which must work harder than usual. This can lead to heart failure, as well as enlargement and other problems of the liver and spleen. When untreated, beta thalassemia major generally results in childhood death usually due to heart failure. Fortunately, in developed countries diagnosis is usually made early, often before symptoms have begun. This allows for treatment with blood transfusion therapy, which can prevent most of the complications of the severe anemia caused by beta thalassemia major. Individuals with beta thalassemia intermedia have a more moderate anemia that may only require treatment with transfusion intermittently, such as when infections occur and stress the body. As a person with beta thalassemia intermedia gets older, however, the need for blood transfusions may increase to the point that they are required on a regular basis. When this occurs their disease becomes more similar to beta thalassemia major. Other genetic and environmental factors can influence the course of the disease as well. For example, co-inheritance of one or two alpha thalassemia mutations can tend to ameliorate some of the symptoms of beta thalassemia disease, which result in part from an imbalance in the amount of alpha- and beta-globin present in the red blood cells.

Hemoglobin H disease

Absence of three alpha globin genes causes an imbalance of alpha and beta globin proteins in the red blood cells. The excess beta globin proteins tend to come together to form hemoglobin H, which is unable to release oxygen to the tissues. In addition, hemoglobin H tends to precipitate out in the cells, causing damage to the red blood cell membrane. When affected individuals are exposed to certain drugs and chemicals known to make the membrane more fragile, the cells are thought to become vulnerable to breakdown in large numbers, a complication called hemolytic anemia. Fever and infection are also considered to be triggers of hemolytic anemia in hemoglobin H disease. This can result in fatigue, paleness, and a yellow discoloration of the skin and whites of eyes called jaundice. Usually, the anemia is mild enough not to require treatment. Severe anemia events may require blood transfusion, however, and are usually accompanied by other symptoms such as dark feces or urine and abdominal or back pain. These events are uncommon in hemoglobin H disease, although they occur more frequently in a more serious type of hemoglobin H disease called hemoglobin H/Constant Spring disease. Individuals effected with this type of hemoglobin H disease are also more likely to have enlargement of and other problems with the spleen.

Alpha thalassemia major

Because alpha globin is a necessary component of all major hemoglobins and some minor hemoglobins, absence of all functioning alpha globin genes leads to serious medical consequences that begin even before birth. Affected fetuses develop severe anemia as early as the first trimester of pregnancy. The placenta, heart, liver, spleen, and adrenal glands may all become enlarged. Fluid can begin collecting throughout the body as early as the start of the second trimester, causing damage to developing tissues and organs. Growth retardation is also common. Affected fetuses usually miscarry or die shortly after birth. In addition, women carrying affected fetuses are at increased risk of developing complications of pregnancy and delivery. Up to 80% of such women develop toxemia, a disturbance of metabolism that can potentially lead to convulsions and coma. Other maternal complications include premature delivery and increased rates of cesarean section, as well as hemorrhage after delivery.

Treatment and management

Beta thalassemia

Individuals with beta thalassemia major receive regular blood transfusions, usually on a monthly basis. This helps prevent severe anemia and allows for more normal growth and development. Transfusion therapy does have limitations, however. Individuals can develop reactions to certain proteins in the blood—called a transfusion reaction. This can make locating appropriately matched donor blood more difficult. Although blood supplies in the United States are very safe, particularly relative to the past and other areas of the world, there remains an increased risk of exposure to blood-borne infection such as hepatitis. Additionally, the body is not able to get rid of the excess iron that accompanies each transfusion. An additional medication called desferoxamine is administered, usually five nights per week over a period of several hours using an automatic pump that can be used during sleep or taken anywhere the person goes. This medication is able to bind to the excess iron, which can then be eliminated through urine. If desferoxamine is not used regularly or is unavailable, iron overload can develop and cause tissue damage and organ damage and failure. The heart, liver, and endocrine organs are particularly vulnerable. Desferoxamine itself may rarely produce allergic or toxic side-effects, including hearing damage. Signs of desferoxamine toxicity are screened for and generally develop in individuals who overuse the medication when body iron levels are sufficiently low. Overall, however, transfusion and desferoxamine therapy has increased the life expectancy of individuals with the most severe types of beta thalassemia major to the fourth or fifth decade. This can be expected to improve with time and increased developments in treatment, as well as for those with more mild forms of the disease.

New treatments offer additional options for some individuals with beta thalassemia major. There are various medications that target the production of red blood cells (i.e. erythropoeitin) or fetal hemoglobin (i.e. hydroxyurea and butyrate). Their effectiveness in ameliorating the severity of beta thalassemia is currently being investigated. Another promising new treatment is bone marrow transplantation, in which the bone marrow of an affected individual is replaced with the bone marrow of an unaffected donor. If successful, this treatment can provide a cure. However, there is an approximately 10-15% chance the procedure could be unsuccessful (i.e. the thalassemia returns), result in complications (i.e. graft-versus-host disease), or result in death. The risk for specific individuals depends on current health status, age, and other factors. Because of the risks involved and the fact that beta thalassemia is a treatable condition, transplant physicians require a brother or sister donor who has an identically matched tissue type, called HLA type. HLA type refers to the unique set of proteins present on each individual's cells, which allows the immune system to recognize "self" from "foreign." HLA type is genetically determined, so there is a 25% chance for two siblings to be a match. Transplant physicians and researchers are also investigating ways to improve the safety and effectiveness of bone marrow transplantation. Using newborn sibling umbilical cord blood—the blood from the placenta that is otherwise discarded after birth but contains cells that can go on to make bone marrow—seems to provide a safer and perhaps more effective source of donor cells. Donors and recipients may not have to be perfect HLA matches for a successful transplant using cord blood cells. Trials are also underway to determine the effectiveness of "partial transplants," in which a safer transplant procedure is used to replace only a percentage of the affected individual's bone marrow. Other possible treatments on the horizon may include **gene therapy** techniques aimed at increasing the amount of normal hemoglobin the body is able to make.

Hemoglobin H disease

Hemoglobin H disease is a relatively mild form of thalassemia that may go unrecognized. It is not generally considered a condition that will reduce one's life expectancy. Education is an important part of managing the health of an individual with hemoglobin H disease. It is important to be able to recognize the signs of severe anemia that require medical attention. It is also important to be aware of the medications, chemicals, and other exposures to avoid due to the theoretical risk they pose of causing a severe anemia event. When severe anemia occurs, it is treated with blood transfusion therapy. For individuals with hemoglobin H disease, this is rarely required. For those with the hemoglobin H/Constant Spring form of the disease, the need for transfusions may be intermittent or ongoing, perhaps on a monthly basis and requiring desferoxamine treatment. Individuals with this more severe form of the disease may also have an increased chance of requiring removal of an enlarged and/or overactive spleen.

Alpha thalassemia major

Because alpha thalassemia major is most often a condition that is fatal in the prenatal or newborn period, treatment has previously been focused on identifying affected pregnancies in order to provide appropriate management to reduce potential maternal complications. Pregnancy termination provides one form of management. Increased prenatal surveillance and early treatment of maternal complications is an approach that

is appropriate for mothers who wish to continue their pregnancy with the knowledge that the baby will most likely not survive. In recent years, there have been a handful of infants with this condition who have survived long-term. Most of these infants received experimental treatment including transfusions before birth, early delivery, and even bone marrow transplantation before birth, although the latter procedure has not yet been successful. For those infants that survive to delivery, there seems to be an increased risk of developmental problems and physical effects, particularly heart and genital malformations. Otherwise, their medical outlook is similar to a child with beta thalassemia major, with the important exception that ongoing, life-long blood transfusions begin right at birth.

Prognosis

As discussed above, the prognosis for individuals with the most serious types of thalassemia has improved drastically in the last several years following recent medical advances in transfusion, chemo-, and transplantation therapy. Advances continue and promise to improve the life expectancy and quality of life further for affected individuals.

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Children's Blood Foundation. 333 East 38th St., Room 830, New York, NY 10016-2745. (212) 297-4336. cfg@nyh.med.cornell.edu.

Cooley's Anemia Foundation, Inc. 129-09 26th Ave. #203, Flushing, NY 11354. (800) 522-7222 or (718) 321-2873. <http://www.thalassemia.org>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

National Heart, Lung, and Blood Institute. PO Box 30105, Bethseda, MD 20824-0105. (301) 592-8573. nhlbiinfo@rover.nhlbi.nih.gov. <http://www.nhlbi.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Jennifer Bojanowski, MS, CGC

Thalidomide embryopathy

Definition

The term thalidomide embryopathy (TE) is used to describe a specific pattern of birth defects caused by a mother's use of the drug thalidomide during her pregnancy. The drug is able to cross the placenta and reaches the developing embryo, causing parts of the embryo's body to form abnormally. The most common birth defects observed in infants with TE include structural abnormalities of the arms, legs, ears, and eyes, although other organs may also be affected. The most harmful time to use thalidomide is during the first three to six weeks of pregnancy.

Description

Thalidomide was originally marketed in Germany in October 1957 as a safe, inexpensive, and effective sedative. Its use was later expanded to include treatment of insomnia, anxiety, upset stomach, and morning sickness during pregnancy. Prior to its release onto the market, thalidomide had been tested in rodents and had been deemed safe; human studies were not performed. It was made available in at least 46 countries. However, the drug was never approved for marketing in the United States due to concerns about the medication's potential side effects, one of which, peripheral neuropathy, was first recognized in 1960. Symptoms of peripheral neuropathy, or nerve damage, include burning, numbness, or tingling in the arms, legs, hands, or feet. The damage may not be reversible even after stopping the medication. Early in the 1960s, an increased number of infants with severe abnormalities of the arms and legs were observed in Germany, Great Britain, and Australia. Once it became clear that the mothers of these infants had taken thalidomide while pregnant, a connection was made between the drug and the birth defects. In 1961, the drug was withdrawn from the worldwide market. It has since become known as a powerful human **teratogen**, a drug or other agent proven to cause birth defects. The experience with thalidomide also led to greater overall attention to the potential effects of drug and other environmental exposures on a developing fetus, and to improved legislation regarding testing requirements before a new drug is released to the public.

Although the use of thalidomide decreased dramatically after 1961, it remained available in the United States and other countries on a "compassionate use" basis: physicians could obtain special permission to treat ill patients they believed could significantly benefit from the drug. Over time, it became clear that thalidomide is effective in the treatment of a number of medical conditions. This surprising resurgence of thalidomide has, in turn, led to concern over the possibility of another generation of children born with thalidomide-related birth defects. The manufacturer of thalidomide, Celgene Corporation, is working in close partnership with the U.S. Food and Drug Administration (FDA) to tightly control the use of the drug and to maintain close follow-up on all individuals to whom it is prescribed. The drug is marketed under the brand name Thalomid.

Limb abnormalities are the most readily identified, and most well known, type of birth defect caused by prenatal thalidomide exposure. However, other types of physical problems may also occur in an exposed infant. In addition to limb abnormalities, TE may include abnormalities of the ears, eyes, kidneys, heart, intestinal tract, and nervous system. Mental retardation has been reported in approximately 5% of older individuals with TE.

Genetic profile

TE is not an inherited medical condition. However, thalidomide is a known teratogen. Therefore, women who use this medication while pregnant are at risk of having infants with physical, and possibly mental, birth defects. A woman who does not use thalidomide during pregnancy cannot have a child with TE. As of 2001, it is still not entirely clear how thalidomide causes birth defects. One hypothesis is that the drug prevents formation of new blood vessels. Research is continuing in this area.

Demographics

It is estimated that 10,000–12,000 infants were born with birth defects consistent with TE following its initial period of use in the late 1950s to early 1960s. According to the Teratology Society 1998 Public Affairs Symposium, approximately 40%, or roughly 5,000, of the affected individuals survived.

In July 1998, the FDA approved the use of thalidomide in the United States, under a very tightly controlled protocol, for the treatment of erythema nodosum leprosum

KEY TERMS

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

Erythema nodosum leprosum—A complication of leprosy characterized by development of painful small swellings due to inflammation of a blood or lymph vessel. It is often accompanied by inflammation of a nerve or nerves, causing decreased function of the affected area.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Immunologic—Related to immunology, the study of how the body's immune system fights disease. Many immunologic disorders are characterized by the body's use of antibodies.

Insomnia—An inability to either fall or stay asleep, particularly at a time of day when sleep is expected. A number of medications are available, and may be used, for treatment.

Leprosy—A chronic, contagious skin and nervous system disease that leads, in the more serious form, to numbness, muscle weakness, and paralysis. Leprosy is sometimes referred to as Hansen's disease.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Sedative—Medication that has a soothing or tranquilizing effect.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

(ENL), a painful skin complication of leprosy. The drug has been available in South America, an area where leprosy is more common than in the United States. Reports of thalidomide-affected South American infants were published as recently as 1996.

As of 2001, medical researchers are studying whether or not thalidomide may be effective in the treatment of other medical conditions, including certain skin and immunologic disorders, certain complications associated with human immunodeficiency virus (HIV) infection, and certain cancers. Although pregnancies among female patients with any of these conditions may be rare, unintended pregnancies will occur and will be at risk for fetal abnormalities if the mothers are taking thalidomide.

Signs and symptoms

TE includes a spectrum of physical abnormalities, all of which may occur at various levels of severity. An affected individual may not have every type of birth defect. All affected infants, however, have been exposed to thalidomide in early pregnancy, a time when the organs and body of an embryo are rapidly developing. Although use of thalidomide at any point in pregnancy is strongly discouraged, women who use the drug during the first six weeks of pregnancy are at the greatest risk of having children with birth defects. Rigorous control of the drug is necessary since many pregnancies are unplanned and may go unrecognized until after the drug exposure has occurred.

The clinical features of TE include:

Limb defects

The most well known type of abnormality is referred to as phocomelia. Phocomelia occurs when most of the bones in the arms or legs are missing, and the hand or foot is attached directly to the body, similar to a flipper. Radial aplasia, or absence of the thumb and connecting bone in the forearm (radius), is another common abnormality. Abnormalities of the digits include a triphalangeal thumb (three small bones in the thumb, rather than two, such that the thumb looks like a finger), or an absent (hypoplastic) thumb only. Similar defects of the legs may also occur. Frequently, affected infants have abnormalities on both sides of their bodies, involving all four extremities.

Ears

Malformations of the ears are common. These range from complete absence of the ear (severe microtia, also sometimes referred to in the medical literature as anotia) to mild changes in the appearance of the external ear. Abnormalities of the inner ear frequently cause deafness.

Inner ear malformations may occur even if the external ear appears normal.

Eyes

A range of eye abnormalities have been reported, including a very small eye (microphthalmos), **glaucoma**, strabismus, cataract, and abnormal production of tears.

Other

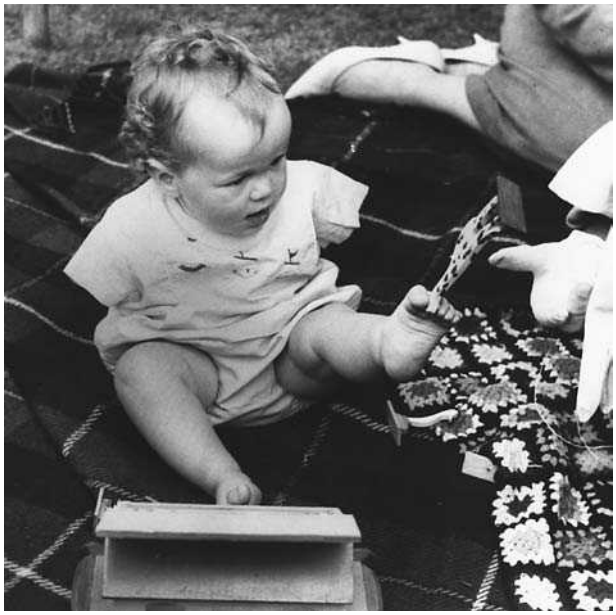
- Structural heart defects.
- Kidney malformations, most often an absent or misplaced kidney.
- Abnormalities of the intestinal system.
- Structural defects of the spine and chest.
- Central nervous system abnormalities, such as mental handicap, described in a small percentage of older individuals with TE.
- Paralysis of the nerves of the face on either one side, both sides equally, or both sides but asymmetrically.
- An increased risk for early infant death, particularly among those infants with severe abnormalities of their internal organs.

Diagnosis

Exposure to thalidomide during the first six weeks of pregnancy poses a significantly increased risk of having a child with TE. It is important to note that the exact dosage of the drug during this period is irrelevant. Thalidomide is rapidly broken down in the mother's body and is therefore able to reach her developing embryo quickly. There is no direct genetic test to accurately diagnose all thalidomide-related birth defects before delivery. However, prenatal ultrasound examinations may be used to identify major structural abnormalities, such as those involving the limbs, heart, kidneys, and intestinal tract. A careful physical examination by a knowledgable and experienced physician(s) is warranted after birth to document the nature and severity of any thalidomide-induced birth defects. Additional studies, such as hearing evaluations, are also indicated.

Treatment and management

Management of the individual with TE is primarily symptomatic. Specialized medical care, such as heart surgery, may be necessary in certain situations, and should be determined on a case-by-case basis. Deaf individuals may require hearing aids and/or will need to learn sign language. Severe limb abnormalities may lead to the use of a wheelchair or other device to assist in mobility.



Thomas Yendell, a baby affected by thalidomide, picks up a toy with his feet. *(AP/Wide World Photos)*

In order to try to minimize the number of future children born with TE, the drug manufacturer and the FDA implemented the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program in 1998. The goals of the program are three-fold: (1) to limit the risk of fetal exposure to thalidomide; (2) to enforce universal compliance of patients, physicians, and pharmacists with the designated components of the program; and, (3) to support appropriate, controlled use of the drug. To achieve this, the S.T.E.P.S. program requires informed consent from all patients to whom the drug will be given. Face-to-face counseling, a patient information booklet, and videotape are all used to review the potential benefits and side effects of the medication. Plans for birth control (contraception) and/or abstinence from sexual intercourse are also discussed. All women of childbearing age must agree to a pregnancy test prior to receiving their medication and at frequent intervals during treatment. Two methods of birth control are additionally required. Physicians who will be prescribing thalidomide must be registered in the S.T.E.P.S. program and must agree to follow each step of the program. Prescriptions may only be filled at registered pharmacies. No more than a one-month supply of the medication may be provided at one time; there are no automatic refills. It is recommended that women receive only a one-week supply, particularly during the first four weeks of treatment. Weekly refills are granted only with proof from a physician of a negative pregnancy test. In the event that a woman becomes pregnant, or suspects that she may be pregnant, an immediate referral is made for

medical evaluation. Follow-up care is provided, and a database of all patients taking thalidomide is maintained.

Despite this unprecedented level of strict control, the S.T.E.P.S. program is unlikely to completely prevent the birth of *every* child in the United States with TE. Other countries in which the drug has been approved for use have been encouraged to develop similar methods to follow outcomes of pregnancies exposed to thalidomide. In the meantime, research is continuing to find drugs that will be as effective as thalidomide without the same dangers to embryonic development.

Prognosis

There is no data addressing long-term survival rates among individuals with TE. Nonetheless, the presence and severity of thalidomide-related birth defects, particularly those involving the heart, would be expected to have the greatest impact on longevity. Severe heart malformations that cannot be corrected by surgery are likely to lead to early death. In the absence of such abnormalities, a normal lifespan is anticipated.

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Terri A. Knutel, MS, CGC

Thanatophoric dysplasia

Definition

Thanatophoric **dysplasia** is one of the most common and most severe forms of dwarfism. Affected infants have marked shortening of their arms and legs, a small chest, and a relatively large head. Most die within a few days after birth; longer-term survivors have been reported but are rare.

Description

Thanatophoric dysplasia (TD) was first described in 1967 to refer to infants with a severe form of dwarfism who died within the first hours of life. The word "thanatophoric" is derived from the Greek word, *thanatophorus*, which means "death-bringing." The term thanatophoric dwarfism is occasionally used. However, over time, the word dysplasia, which refers to any disorder in growth, has become the preferred terminology.

Two distinct types of TD were delineated in 1987. Affected infants are divided based on their particular combination of physical features and skeletal findings. While all individuals with TD have micromelia, or abnormally small or short arms and legs, differences in the length and shape of the femurs, the bones of the thigh, can be used to distinguish between TD types 1 (TD1) and 2 (TD2). Infants with TD1 have curved, "telephone-receiver"-like femurs. In contrast, the femurs of infants with TD2 are longer and straighter.

The presence of skull abnormalities is another important distinction between the two types: infants with TD2 typically have a severe abnormality of the bones of the skull, referred to as cloverleaf skull or kleeblattschadel anomaly. The skull of a normal infant is composed of several segments of bone, some of which are completely joined together, or fused, by the time of delivery. Their lines of fusion are referred to as sutures. Some sutures are only partially fused, leaving soft, skin-covered openings that will gradually close over the first year of life. Premature closure of these sutures leads to a condition called craniosynostosis. **Craniosynostosis** often leads to an abnormal skull shape and, if not eventually corrected by surgery, prevents normal growth of the brain. The most extreme form of craniosynostosis, as seen in infants with TD2, causes a severely abnormal skull whose shape resembles that of a cloverleaf. Although milder forms of craniosynostosis may be found in infants with TD1, cloverleaf skull is not typically present.

Other bone abnormalities occur in both TD types 1 and 2, including an abnormal shape of and spacing between the bones in the spine (vertebrae), shortened

ribs, and small pelvic bones. Most of the other organs of the body, with the exception of the brain, are normal, although occasional abnormalities of the kidneys have been reported. A variety of abnormal changes in the structure of the brain have been described. The small number of children with TD who have survived past infancy have been severely mentally and physically handicapped.

The most common cause of death among individuals with TD is respiratory insufficiency. The small chest and, consequently, limited growth of the lungs, are the primary reasons for the breathing problems. However, associated abnormalities of the central nervous system are most likely also involved since these interfere with the body's ability to regulate normal breathing.

Genetic profile

Both types of thanatophoric dysplasia occur as sporadic, autosomal dominant conditions. Only one copy of the altered **gene** causing TD needs to be present in order for the condition to occur. Males and females are equally likely to be affected. The parents of an affected child do not have TD and are normal. Thus, it is believed that, in most cases, a new genetic mutation, or change, causing TD occurred in either the egg or sperm cell that gave rise to that particular pregnancy. Such a mutation cannot be made to happen; it occurs simply by chance. A very low risk of recurrence, or chance of another affected child in a future pregnancy, would be expected. Unfortunately, families have been described with more than one child with TD. The most likely explanation in these families is gonadal mosaicism.

Gonadal mosaicism occurs when a normal adult has a mixed population of cells in his or her gonads (testes or ovaries). All of the other cells in that individual's body are presumably normal. Most sperm or egg cells from these gonads would be normal and would not have a TD mutation; however, an unknown percentage would carry the mutation. As a result, even though the parent would be normal, he or she could, with the same or a different partner, have another child with TD. It is virtually impossible to prove whether or not a parent has gonadal mosaicism. Even so, all parents of an affected child are counseled that gonadal mosaicism in one of them is a possibility.

Thanatophoric dysplasia is caused by mutations in the fibroblast growth factor receptor 3 gene (FGFR3), located on the short arm of chromosome 4 at band 16.3 (abbreviated as 4p16.3). The fibroblast growth factors are a family of important proteins in the human body. They are involved in the production of new cells and new blood vessels as well as in the healing of wounds. Mutations in each of the fibroblast growth factor genes (FGFR1, 2, and 3) have been linked to a variety of genetic conditions. The FGFR3 protein is primarily found in cartilage and the central nervous system. Different mutations in the FGFR3 gene have been associated with other skeletal dysplasias, most notably **achondroplasia** and **hypochondroplasia**.

As might be expected, different mutations in FGFR3 have been found in patients with TD1 versus those with TD2. As of 2001, a wider variety of mutations have been identified among infants with TD1. One predominant mutation has been present in nearly all cases of TD2 studied so far. Regardless of the specific mutation, the net effect of each of the mutations in both TD1 and TD2 is the same: the linear growth of bone is prevented, resulting in very short, small bones.

Demographics

Thanatophoric dysplasia is the most common lethal skeletal dysplasia, with an estimated incidence of one in

KEY TERMS

Acondroplasia—An autosomal dominant form of dwarfism caused by a defect in the formation of cartilage at the ends of long bones. Affected individuals typically have short limbs, a large head with a prominent forehead and flattened profile, and a normal-sized trunk.

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Hypochondroplasia—An autosomal dominant form of dwarfism whose physical features are similar to those of achondroplasia but milder. Affected individuals have mild short stature and a normal facial appearance.

35,000–50,000 births. It has been described in all races and ethnic groups.

Signs and symptoms

Infants with TD are typically identified either during pregnancy or at the time of birth. Affected pregnancies are often complicated by polyhydramnios, or excess amniotic fluid around the fetus. As a result, the mother often appears more pregnant than she actually is. It is common for a prenatal ultrasound examination to be performed to rule out a fetal birth defect as the cause. The serious limb abnormalities typical of TD are often identified in this way. Polyhydramnios may also lead to an increased chance of early labor and premature delivery. The pregnant woman may require more intensive monitoring of her pregnancy.

At birth, newborns with TD typically have a very large head with a prominent forehead, a flattened bridge of the nose, and prominent, bulging eyes. Their limbs are extremely short and are often held extended out from the rest of the body. The neck is short, the chest is narrow, and the belly appears unusually large, giving an overall resemblance to a pear. The shape of the skull may be abnormal due to either cloverleaf skull or a milder form of craniosynostosis. Newborns are often rather floppy, or hypotonic, with poor muscle tone and absent primitive neurologic reflexes. Breathing is very difficult due to the small chest and lungs, often leading to the use of a ventilator to prolong survival.

The physical appearance of individuals with TD who survive the neonatal period does not dramatically change over time. Affected children remain very small and have limited potential to walk or move about unaided. Mental retardation due to structural brain malformations has been reported. Seizures and hearing loss frequently develop.

Diagnosis

Prenatal diagnosis of TD is possible based on ultrasound examination, usually during the second half of pregnancy. However, it is important to realize that many of the physical abnormalities seen in fetuses with TD, such as an enlarged head and shortened long bones, may also be found in fetuses with other forms of skeletal dysplasia. Consequently, while ultrasound may suggest a diagnosis of a skeletal dysplasia, it may not be possible to confirm a diagnosis of TD until after birth.

Upon delivery, a careful examination of the infant should be performed to look for many of the more obvious external features of TD. Radiologic studies are extremely important, particularly to distinguish between TD1 and TD2. X ray will confirm the marked shortening of the long bones, identify curved or straight femurs, document the shape and appearance of the spinal vertebrae, and reveal the extent of craniosynostosis. An autopsy, including x rays, is highly recommended on any stillborn infant with TD to confirm the diagnosis.

Mutation studies by analysis of the FGFR3 gene are being used more often to confirm a diagnosis of TD and to determine TD type. Perhaps the greatest benefit of direct **genetic testing** is for those parents who have been told by a prenatal ultrasound examination that their unborn child has a serious bone dysplasia. An **amniocentesis** for additional genetic studies may be offered. Further clarification of the diagnosis allows for more refined counseling regarding the infant's likely prognosis. Termination of the pregnancy may be an option for some couples. For those couples wishing to continue an affected pregnancy, plans can be made for the remaining prenatal care, especially given the risk for polyhydramnios and/or early labor and delivery. Careful consideration may be given as to the level of intervention and medical care desired for the infant after birth.

Knowledge of the specific TD mutation is also helpful in planning care for any future pregnancy. Despite the sporadic nature of TD, a couple with a history of one affected child has a small risk of having a second affected child due to the possibility of gonadal mosaicism. Prenatal testing in a new pregnancy, such as chorionic villus sampling or amniocentesis, may be offered to look for a TD mutation. However, in order for this to be possible, the TD mutation in the previous child must have been determined.

Studies are ongoing to assess whether or not three-dimensional ultrasound, in contrast to the current, much more widely available, two-dimensional ultrasound, may be used to accurately prenatally diagnosis TD and other skeletal dysplasias. If effective, additional prenatal studies could become less common. However, early results have shown no significant improvement in the detection or diagnosis of TD and related disorders. The present standard of care therefore remains a prenatal ultrasound examination, if available, physical evaluations after delivery, and identification of the underlying genetic mutation, whenever possible.

Treatment and management

The treatment and care of an infant with TD is mainly supportive. The poor prognosis associated with TD should be discussed. Infants who survive the newborn period will require intensive, ongoing medical care.

Prognosis

Nearly all infants with TD, both types 1 and 2, die either at the time of delivery or shortly thereafter due to severe respiratory distress. Aggressive medical treatment after birth has not always helped affected infants live even a short amount of time. Prolonged survival, including one child who, as of 1997, was still alive at the age of nine years, has been reported but is highly unusual. Survival is associated with poor growth and development and with continuing, serious respiratory problems.

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Terri A. Knutel, MS, CGC

Thrichorhinophalangeal syndrome type II

see **Langer-Giedion syndrome**

Thrombasthenia of Glanzmann and Naegeli

Definition

Thrombasthenia of Glanzmann and Naegeli is an extremely rare inherited disorder in which there is abnormal function of a component of the blood called the platelets, leading to abnormalities in blood clotting and increased bleeding.

Description

Blood clotting, or coagulation, is the process by which several factors in the blood stick together to form a physical barrier that prevents bleeding. In response to a disruption in blood flow or bleeding because of injury, several factors in the blood stick together at the site of injury, sealing off the blood vessel and stopping blood loss in a process called hemostasis. If any of the factors that contribute to the process of coagulation and hemostasis are abnormal, dangerous bleeding conditions can result.

One of the factors involved in hemostasis is called the platelet. Platelets are small disc-shaped structures that circulate in the blood stream in an inactive state. When an injury occurs, platelets become activated and stick to fibrous proteins, called fibrinogen, that are also circulating in the blood stream. Because there are multiple sites on the fibrinogen proteins for platelets to bind and vice versa, a cross-linked net or mass called a "platelet plug" is formed which seals off the injury and prevents further bleeding. Next, the platelet mass actively contracts to form an even more solid mass in a process called "clot retraction." Over time, repair cells can use this mass as a scaffolding to lay down new tissue and thereby effect a permanent repair of the injury.

Platelets attach to fibrinogen through the use of specialized sugar-proteins (glycoproteins) that are present on the platelet surface. There are two specific glycoproteins that form a complex responsible for the platelet-fibrinogen interaction: glycoprotein IIb, and glycoprotein IIIa.

The platelet disorder thrombasthenia of Glanzmann and Naegeli (TGN) results from an inherited defect in the glycoprotein IIb/IIIa complex (GP IIb/IIIa). As a result of this glycoprotein defect, platelets fail to stick to fibrinogen, leading to defective hemostasis and prolonged bleeding. TGN is sometimes subdivided into different groups: type I, in which there is no functional GP IIb/IIIa; type II, in which small amounts of working GP IIb/IIIa can be detected; and variant thrombasthenia, in which the amount of working GP IIb/IIIa may vary.

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Coagulation—The process by which a liquid becomes a solid, as in blood clotting.

Fibrinogen—A fibrous protein that circulates in blood and participates in blood clotting by attaching to platelets.

Glycoprotein IIb/IIIa (GP IIb/IIIa)—Sugar-proteins on the surface of platelets that bind to the fibrous protein, fibrinogin. These sugar-proteins are defective in Glanzmann's thrombasthenia.

Hemostasis—The arrest of bleeding by blood coagulation.

Mutant—A change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

Transfusion—The injection of a component of the blood from a healthy person into the circulation of a person who is lacking or deficient in that same component of the blood.

Thrombasthenia of Glanzmann and Naegeli has also been referred to by other names, including: Glanzmann's thrombasthenia, diacyclothrombopathia IIb-IIIa, Glanzmann disease, and glycoprotein complex IIb/IIIa deficiency.

TGN was first described by the Swiss physician Edward Glanzmann in 1918. Glanzmann used the term, "thrombasthenia," meaning "weak platelets," because clots from patients with the disorder did not retract well. Although the disease is exceedingly rare, platelets taken from people with the disease have been very useful in the research that first discovered how normal platelets function.

Genetic profile

TGN is a genetic condition and can be inherited or passed on in a family. The disorder results from any number of different mutations that can occur in either the **gene** for glycoprotein IIb or the gene for glycoprotein IIIa (both located on chromosome 17, locus 17q21.32), with defects split equally between the two genes.

In the majority of cases, it appears that the genetic abnormality for the disorder is inherited as an autosomal recessive trait, meaning that two abnormal genes are needed to display the disease. A person who carries one abnormal gene does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to his or her children, who must inherit one abnormal gene from each parent to display the disease. People who are carriers of the abnormal gene appear to have only half-normal amounts of working GP IIb/IIIa, which is still sufficient for normal platelet function.

There are reports of a few families in which the defect is inherited in an autosomal dominant fashion. In this pattern of **inheritance**, only one abnormal gene is needed to display the disease, and the chance of passing the gene to offspring is 50%.

Demographics

TGN is exceedingly rare, with less than 1,000 cases identified between 1962 and 2000. There are several groups in which the majority of cases of thrombasthenia have been discovered, including Iraqi Jews, Arabs living in Israel and Jordan, populations of south India, and French Gypsies of the Manouche tribe.

Signs and symptoms

Most people with TGN will have a major bleeding event before the age of five. Common manifestations of the disease include nose bleeds, bleeding from the gums, or skin rashes caused by bleeding into the skin (known as purpura or petechiae). Larger amounts of bleeding into underlying tissue may result in diffuse black bruises, usually seen on the arms and the legs. Normal handling of infants can cause superficial bruises and may be mistaken for abuse. As a result of chronic bleeding, patients may have lower amounts of red blood cells in their blood (anemia) and suffer from iron deficiencies. Rarely, there may be bleeding into the joints, causing disfiguration. Bleeding after traumatic accidents or after surgical operations and dental procedures may be profuse and require vigorous medical treatment. Prolonged untreated or unsuccessfully treated bleeding associated with TGN may be life-threatening. For reasons which are unclear, severity of bleeding events appears to decrease with increasing age.

There are other concerns when TGN is diagnosed in a woman. Because of the platelet disorder, women may experience particularly heavy menstrual bleeding. In fact, the first occurrence of menstrual bleeding in a young woman may be so severe that it requires prompt medical attention and treatment. Further, pregnancy and delivery represent severe bleeding risks and may not always be manageable with medical treatment.

Diagnosis

TGN is diagnosed through a combination of medical history, physical examination, and laboratory testing. Bleeding episodes and physical manifestations of the disease (as described above) may prompt an investigation for the underlying cause. The presence of a bleeding disorder in more than one close or distant relative is especially important, as it may indicate that a genetic cause of the condition is involved.

Blood tests will reveal normal amounts of platelets. Tests performed with substances that stimulate platelet clumping though GP IIb/IIIa will show minimal effects as a result of the platelet defect. Conversely, tests performed using a different substance, ristocetin, which causes platelet clumping through different mechanisms, will provoke a brisk and appropriate platelet response. Other blood tests will reveal a longer than normal bleeding time, poor clot retraction, and may demonstrate low numbers of red blood cells and iron deficiency.

The diagnosis of TGN is ultimately confirmed by investigating the GP IIb/IIIa glycoprotein complex. Antibodies that are specifically designed to distinguish between normal and abnormal GP IIb/IIIa can be used in a technique known as immunofluorescence (in which the antibody is attached to a fluorescent dye) or a test called a Western blot (in which proteins are first separated by size and then exposed to antibodies). These methods can also be used to detect people who are carriers of a mutant gene for TGN by demonstrating only half-normal amounts of GP IIb/IIIa. Prenatal diagnosis may also be possible but is not recommended as sampling of the blood in an affected fetus may lead to uncontrollable bleeding that could prove fatal.

Treatment and management

Several medications can aid in the treatment of TGN, while others should be avoided. Some patients will demonstrate shortening of their bleeding time with DDAVP, a medication that improves the function of platelets. Women who have heavy bleeding may benefit from birth control pills to prevent their menstrual periods. Nutritional iron supplements may alleviate or prevent the development of iron deficiency and will aid in restoring normal levels of red blood cells. Medications to be avoided are those which interfere with platelet function and predispose to bleeding, including aspirin, ibuprofen and ibuprofen-like drugs, heparin, warfarin, ticlopidine, clopidogrel, abciximab, streptokinase, urokinase, or tissue plasminogen activator.

The treatment of choice for stopping active bleeding is through transfusion of normal platelets that are obtained from donors without the disease. Studies have shown that most people (approximately 85%) with the disorder will require platelet transfusions during their lifetime. For individuals with TGN, transfusion with one unit of platelets for every 11-22 lbs (5-10 kg) of body weight will correct the defect in blood clotting and may be life-saving. Pre-emptive transfusions are especially important before surgical operations or dental procedures. Transfusions should be continued until wound healing is complete.

Over time, platelet transfusion may become less effective. Platelets obtained from donors and given to a patient with TGN are recognized by the immune system as foreign cells. The immune system, in turn, generates antibodies that attach to the donor platelets and impair their function, ultimately leading to their destruction. Because of this unfortunate effect, platelet transfusions are best reserved for life-threatening bleeding or before procedures in which bleeding is likely. Using platelets from donors closely related to the patient may delay the immune response and extend the benefits of transfusion therapy.

Patients with TGN should be followed closely by a hematologist and should be vaccinated against the hepatitis B virus, because of the high risk of exposure to the virus with ongoing blood-product transfusions. Patients should also been seen regularly by a dentist to prevent gum disease that could result in profuse bleeding. **Genetic counseling** can be offered to affected individuals or couples with a family history of the disorder.

Bone marrow transplantation is currently the only curative form of treatment for patients with TGN. However this is generally considered more hazardous than the disease itself, except in exceptional circumstances. In 2000, a multidisciplinary team of scientists, led by a researcher at the Medical College of Wisconsin, was able to correct the GP IIb/IIIa defect in bone marrow cells taken from patients with TGN using advanced **gene therapy** techniques. The researchers are now focusing on applying the technique to lab animals with a form of TGN, but these positive early results give hope for an eventual cure in humans.

Prognosis

Although there is no cure, the prognosis for people with TGN is quite good. Despite the fact that the majority of people with this disorder will require medical treatment to control bleeding, patients rarely die of massive blood loss. Interestingly, the severity of bleeding appears to decrease with increasing age. Barring any catastrophic accident which results in uncontrollable bleeding, lifespan is approximately the same as the general population.

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Oren Traub, MD, PhD

Thrombocytopenia absence of radius syndrome *see* **TAR syndrome**

Tourette syndrome

Definition

Tourette syndrome (TS) is an inherited disorder of the nervous system, characterized by a variable expression of unwanted movements and noises (tics).

Description

The first references in the literature to what might today be classified as Tourette syndrome largely describe individuals who were wrongly believed to be possessed by the devil. In 1885 Gilles de la Tourette, a French neurologist, provided the first formal description of this syndrome, which he described as an inherited neurological condition characterized by motor and vocal tics.

Although vocal and motor tics are the hallmark of Tourette syndrome, other symptoms such as the expression of socially inappropriate comments or behaviors, obsessive compulsive disorder, attention deficit disorder, self injuring behavior, **depression**, and anxiety also appear to be associated with Tourette syndrome. Most research suggests that Tourette syndrome is an autosomal dominant disorder, although a **gene** responsible for Tourette syndrome has not yet been discovered.

Genetic profile

The cause of Tourette syndrome is unknown although some studies suggest that the tics in Tourette syndrome are caused by an increased amount of a neurotransmitter called dopamine. A neurotransmitter is a chemical found in the brain that helps to transmit information from one brain cell to another. Other studies suggest that the defect in Tourette syndrome involves another neurotransmitter called serotonin or involves other chemicals required for normal functioning of the brain.

Most studies suggest that Tourette syndrome is an autosomal dominant disorder with decreased penetrance, although this has not been proven and may not be true in all families. An autosomal dominant disorder results from a change in one copy of a pair of genes. Individuals with an autosomal dominant disorder have a 50% chance of passing on the changed gene to their children. Decreased penetrance means that not all people who inherit the changed gene will develop symptoms. There is some evidence that females who inherit the Tourette syndrome gene have a 70% chance of exhibiting symptoms and males have a 99% chance of having symptoms. It has been suggested that other gene and environmental factors may play a role in the development of symptoms in people who inherit the changed gene but none have been discovered. Some researchers believe that Tourette syndrome has different causes in different individuals or is caused by changes in more than one gene, although these theories are less substantiated. Further research is needed to establish the cause of Tourette syndrome.

Demographics

Tourette syndrome is found in all populations and all ethnic groups but is three to four times more common in

males than females and is more common in children than adults. The exact frequency of Tourette syndrome is unknown but estimates range from 0.05% to 3%.

Signs and symptoms

Motor and vocal tics

The principal symptoms of Tourette syndrome include simple and complex motor and vocal tics. Simple motor tics are characterized by brief muscle contractions of one or more limited muscle groups. An eye twitch is an example of a simple motor tic. Complex motor tics tend to appear more complicated and purposeful than simple tics and involve coordinated contractions of several muscle groups. Some examples of complex motor tics include the act of hitting oneself and jumping. Copropraxia, the involuntary display of unacceptable/obscene gestures, and echopraxia, the imitation of the movement of another individual, are other examples of complex motor tics.

Vocal tics are actually manifestations of motor tics that involve the muscles required for vocalization. Simple vocal tics include stuttering, stammering, abnormal emphasis of part of a word or phrase, and inarticulate noises such as throat clearing, grunts, and high-pitched sounds. Complex vocal tics typically involve the involuntary expression of words. Perhaps the most striking example of this is coprolalia, the involuntary expression of obscene words or phrases, which occurs in fewer than one-third of people with Tourette syndrome. The involuntary echoing of the last word, phrase, sentence or sound vocalized by oneself (phalilalia) or of another person or sound in the environment (echolalia) are also classified as complex tics.

The type, frequency, and severity of tics exhibited varies tremendously between individuals with Tourette syndrome. Tourette syndrome has a variable age of onset and tics can start anytime between infancy and age 18. Initial symptoms usually occur before the early teens and the mean age of onset for both males and females is approximately seven years of age. Most individuals with symptoms initially experience simple muscle tics involving the eyes and the head. These symptoms can progress to tics involving the upper torso, neck, arms, hands, and occasionally the legs and feet. Complex motor tics are usually the latest onset muscle tics. Vocal tics usually have a later onset then motor tics. In some rare cases, people with Tourette syndrome suddenly present with multiple, severe, or bizarre symptoms.

Not only is there extreme variability in clinical symptoms between individuals with Tourette syndrome, but individuals commonly experience a variability in type, frequency, and severity of symptoms within the course of their lifetime. Adolescents with Tourette syndrome often experience unpredictable and variable symptoms, which may be related to fluctuating hormone levels and decreased compliance in taking medications. Adults often experience a decrease in symptoms or a complete end to symptoms.

A number of factors appear to affect the severity and frequency of tics. Stress appears to increase the frequency and severity of tics while concentration on another part of the body that is not taking part in a tic can result in the temporary alleviation of symptoms.

KEY TERMS

Attention deficit disorder (ADD)—Disorder characterized by a short attention span, impulsivity, and in some cases hyperactivity.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Coprolalia—The involuntary expression of obscene words or phrases.

Copropraxia—The involuntary display of unacceptable/obscene gestures.

Decreased penetrance—Individuals who inherit a changed disease gene but do not develop symptoms.

Dysphoria—Feelings of anxiety, restlessness, and dissatisfaction.

Echolalia—Involuntary echoing of the last word, phrase, or sentence spoken by someone else or sound in the environment.

Echopraxia—The imitation of the movement of another individual.

Neurotransmitter—Chemical in the brain that transmits information from one nerve cell to another.

Obsessive compulsive disorder (OCD)—Disorder characterized by persistent, intrusive, and senseless thoughts (obsessions) or compulsions to perform repetitive behaviors that interfere with normal functioning.

Phalilalia—Involuntary echoing of the last word, phrase, sentence, or sound vocalized by oneself.

Tic—Brief and intermittent involuntary movement or sound.

Relaxation, following attempts to suppress the occurrence of tics, may result in an increased frequency of tics. An increased frequency and severity of tics can also result from exposure to drugs such as steroids, cocaine, amphetamines, and caffeine. Hormonal changes such as those that occur prior to the menstrual cycle can also increase the severity of symptoms.

Other associated symptoms

People with Tourette syndrome are more likely to exhibit non-obscene, socially inappropriate behaviors such as expressing insulting or socially unacceptable comments or socially unacceptable actions. It is not known whether these symptoms stem from a more general dysfunction of impulse control that might be part of Tourette syndrome.

Tourette syndrome appears to also be associated with attention deficit disorder (ADD). ADD is a disorder characterized by a short attention span and impulsivity and in some cases hyperactivity. Researchers have found that 21–90% of individuals with Tourette syndrome also exhibit symptoms of ADD, whereas 2–15% of the general population exhibit symptoms of ADD.

People with Tourette syndrome are also at higher risk for having symptoms of obsessive compulsive disorder (OCD). OCD is a disorder characterized by persistent, intrusive, and senseless thoughts (obsessions) or compulsions to perform repetitive behaviors that interfere with normal functioning. A person with OCD, for example, may be obsessed with germs and may counteract this obsession with continual hand washing. Symptoms of OCD are present in 1.9–3% of the general population, whereas 28–50% of people with Tourette syndrome have symptoms of OCD.

Self-injurious behavior (SIB) is also seen more frequently in those with Tourette syndrome. Approximately 34–53% of individuals with Tourette syndrome exhibit some form of self-injuring behavior. The SIB is often related to OCD but can also occur in those with Tourette syndrome who do not have OCD.

Symptoms of anxiety and depression are also found more commonly in people with Tourette syndrome. It is not clear, however, whether these symptoms are symptoms of Tourette syndrome or occur as a result of having to deal with the symptoms of moderate to severe Tourette syndrome.

People with Tourette syndrome may also be at increased risk for having learning disabilities and personality disorders and may be more predisposed to behaviors such as aggression, antisocial behaviors, severe temper outbursts, and inappropriate sexual behavior. Further controlled studies need to be performed, however, to ascertain whether these behaviors are symptoms of Tourette syndrome.

Diagnosis

Tourette syndrome cannot be diagnosed through a blood test. The diagnosis is made through observation and interview of the patient and discussions with other family members. The diagnosis of Tourette syndrome is complicated by a variety of factors. The extreme range of symptoms of this disorder makes it difficult to differentiate Tourette syndrome from other disorders with similar symptoms. Diagnosis is further complicated by the fact that some tics appear to be within the range of normal behavior. For example, an individual who only exhibits tics such as throat clearing and sniffing may be misdiagnosed with a medical problem such as allergies. In addition, bizarre and complex tics such as coprolalia may be mistaken for psychotic or "bad" behavior. Diagnosis is also confounded by individuals who attempt to control tics in public and in front of health care professionals and deny the existence of symptoms. Although there is disagreement over what criteria should be used to diagnosis Tourette syndrome, one aid in the diagnosis is the *Diagnostical and Statistical Manual of Mental Disorders* (*DSM-IV*). The *DSM-IV* outlines suggested diagnostic criteria for a variety of conditions including Tourette syndrome such as:

- Presence of both motor and vocal tics at some time during the course of the illness.
- The occurrence of multiple tics nearly every day through a period of more than one year, without a remission of tics for a period of greater than three consecutive months.
- The symptoms cause distress or impairment in functioning.
- Age of onset of prior to 18 years of age.
- The symptoms are not due to medications or drugs and are not related to another medical condition.

Some physicians critique the *DSM-IV* criteria, citing that they do not include the full range of behaviors and symptoms seen in Tourette syndrome. Others criticize the criteria since they limit the diagnosis to those who experience a significant impairment, which may not be true for individuals with milder symptoms. For this reason many physicians use their clinical judgment as well as the *DSM-IV* criteria as a guide to diagnosing Tourette syndrome.

Treatment and management

There is no cure for Tourette syndrome, and treatment involves the control of symptoms through educa-

tional and psychological interventions and/or medications. The treatment and management of Tourette syndrome varies from patient to patient and should focus on the alleviation of the symptoms that are most bothersome to the patient or that cause the most interference with daily functioning.

Psychological and educational interventions

Psychological treatments such as counseling are not generally useful for the treatment of tics but can be beneficial in the treatment of associated symptoms such as obsessive-compulsive behavior and attention deficit disorder. Counseling may also help individuals to cope better with the symptoms of this disorder and to have more positive social interactions. Psychological interventions may also help people cope better with stressors that can normally be triggers for tics and negative behaviors. Relaxation therapies may, however, increase the occurrence of tics. The education of family members, teachers, and peers about Tourette syndrome can be helpful and may help to foster acceptance and prevent social isolation.

Medications

Many people with mild symptoms of Tourette syndrome never require medications. Those with severe symptoms may require medications for all or part of their lifetime. The most effective treatment of tics associated with Tourette syndrome involves the use of drugs such as Haloperidol, Pimozide, Sulpiride, and Tiapride, which decrease the amount of dopamine in the body. Unfortunately, the incidence of side effects, even at low dosages, is quite high. The short-term side effects can include sedation, dysphoria, weight gain, movement abnormalities, depression, and poor school performance. Long-term side effects can include phobias, memory difficulties, and personality changes. These drugs are therefore better candidates for short-term rather than long-term therapy.

Tourette syndrome can also be treated with other drugs such as clonidine, clonazepam, and risperidone, but the efficacy of these treatments is unknown. In many cases, treatment of associated conditions such as ADD and OCD is often more of a concern than the tics themselves. Clonidine used in conjunction with stimulants such as Ritalin may be useful for treating people with Tourette syndrome who also have symptoms of ADD. Stimulants should be used with caution in individuals with Tourette syndrome since they can sometimes increase the frequency and severity of tics. OCD symptoms in those with Tourette syndrome are often treated with drugs such as Prozac, Luvox, Paxil, and Zoloft.

In many cases the treatment of Tourette syndrome with medications can be discontinued after adolescence. Trials should be performed through the gradual tapering off of medications and should always be done under a doctor's supervision.

Prognosis

The prognosis for Tourette syndrome in individuals without associated psychological conditions is often quite good, and only approximately 10% of Tourette syndrome individuals experience severe tic symptoms. Approximately 30% of people with Tourette syndrome will experience a decrease in the frequency and severity of tics and another 30–40% will experience a complete end of symptoms by late adolescence. The other 30–40% will continue to exhibit moderate to severe symptoms in adulthood. There does not appear to be a definite correlation between the type, frequency, and severity of symptoms and the eventual prognosis. Patients with severe tics may experience social difficulties and may isolate themselves from others in fear of shocking and embarrassing them. People with Tourette syndrome who have other symptoms such as obsessive compulsive disorder, attention deficit disorder, and self-injurious behavior usually have a poorer prognosis.

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National Tourette Syndrome Association, Inc. 42-40 Bell Blvd., Bayside, NY 11361-2820. (718) 224-2999. Fax: (718) 279-9596. tourette@ix.netcom.com.

Tourette Syndrome Foundation of Canada. 194 Jarvis Street, #206, Toronto, ONT M5B 2B7. Canada (800) 361-3120. tsfc.org@sympatico.ca. <http://www.tourette.ca>.

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Lisa Maria Andres, MS, CGC

Translation *see* **Chromosomal abnormalities**

Treacher Collins syndrome

Definition

Treacher Collins syndrome (TCS) is a genetic disorder involving abnormal facial development. Individuals with TCS have underdevelopment of the jawbone, cheekbones, ears, and eye area. These features range widely from mild to severe. Intelligence and lifespan are usually normal.

Description

TCS was first described by E. Treacher Collins in 1900 after observation of two individuals with similar facial abnormalities. In 1940, Franceschetti and Klein gave TCS another name, mandibulofacial dysostosis. TCS is also sometimes called Franceschetti-Klein syndrome or Franceschetti syndrome.

The features of TCS result from a problem in early embryonic development. After an embryo forms, there are cells that are unspecialized and have the ability to develop into any type of cell in any part of the body (neural crest cells). Early in development, the neural crest cells travel to different areas of the embryo and specialize to become a specific type of cell for a specific organ or body part. The branchial arches is the area where neural crest cells specialize to develop the bone structure and features of the face. In individuals with TCS there is thought to be an error in the movement of the neural crest cells to the branchial arches or in the specialization of those cells once they reach the branchial arches. The result is underdevelopment of the facial bones, eyes, and ears.

Individuals with mild features of TCS may go undiagnosed. Sometimes adults do not know they have TCS until they have a child with more noticeable features. This can cause feelings of guilt for the parent. Children with more moderate to severe features of TCS look strikingly different and may be teased or shunned. These children are at risk for psychological stress and low self-esteem. Even adults with TCS who are productive and successful may battle issues of social stigma and low self-esteem regarding their facial differences.

Genetic profile

TCS is an autosomal dominant condition. Children of an affected parent have a 50% chance of inheriting the disorder. Males and females are affected equally. The severity of symptoms ranges widely, even among members of the same family. Therefore, the severity of a child's features cannot be predicted by the features of the affected parent.

About 40% of babies born with TCS have one affected parent. The other 60% are assumed to have a new, sporadic **gene mutation** (alteration). If a child has a new mutation (one that is not carried by the parents) then his or her siblings will have an extremely low chance of also having TCS. When a baby with TCS is born to seemingly normal parents, it is important to examine both parents carefully for mild features of TCS in order to give them accurate recurrence risks.

The **gene** for TCS is on chromosome 5 and is called TCOF1. This gene produces a protein that has been named treacle. Disease-causing TCOF1 mutations result in absent or inactive treacle. The exact role of treacle is not known but it is thought to be involved in early embryo neural crest cell movement or specialization in the branchial arches.

Demographics

TCS is rare and affects an estimated one in 25,000 to 50,000 live births.

Signs and symptoms

TCS is described as a craniofacial condition because its features are all related to the head and face. The overall head size may be smaller than average (microcephaly). The outer corners of the eyes slant

downward. There may be colobomas on the lower eyelids, giving the lids a droopy appearance. The bridge of the nose is usually wide. Most individuals with TCS have underdeveloped cheekbones (malar bones) which give that area of the face a flat or sunken appearance. The lower jaw and chin are usually small and retroverted (jawbone points downward toward the neck instead of pointing out perpendicular to the neck). Many individuals also have a large mouth. Cleft palate (with or without cleft lip) is seen in one-quarter to one-third of patients with TCS.

Ear abnormalities are also common in TCS. The ears may be low-set, small, misshapen, or absent. For this reason, hearing loss or deafness is a common feature of TCS. The hearing loss is usually due to abnormalities in the middle ear structures rather than the outer ear structures.

Infants with moderate or severe malar bone underdevelopment may have compressed airways. These babies can have problems breathing after birth and may need a respirator or tracheostomy. A small, retroverted jaw and chin can cause feeding problems that may warrant a feeding tube.

The severity of features present at birth remains constant throughout life. TCS does not get progressively better or worse as an individual ages.

Diagnosis

The diagnosis of TCS is usually made by physical examination and identification of the typical facial features. Computerized tomography (CT scans) can be used to determine the degree of underdevelopment of the facial bone structure.

There are other syndromes that have facial appearances that resemble TCS. A complete physical examination of other body systems can help to establish a diagnosis of TCS. TCS can be distinguished from Nager syndrome and Miller syndrome if no abnormalities are present in the hands or arms. TCS can be distinguished from oculoauriculovertebral (OAV) conditions (for example, **Goldenhar syndrome**) because facial involvement is bilateral (affecting both sides of the face) and the spinal column is normal.

If there are several people in a family with TCS, genetic linkage studies can be performed. Linkage studies require blood samples from many family members, both affected and unaffected. Markers on the TCOF1 gene are analyzed and compared to determine which gene version is shared by affected family members. The disease-causing gene should be present in all affected family members and absent from all unaffected members. Linkage studies can be performed on an unborn baby to determine if the baby inherited the family's disease-causing gene. Prenatal ultrasound can also be used to look for facial features of TCS. While there have been reports of prenatal diagnosis of TCS with ultrasound only, babies with mild features may appear normal. Detection may also depend on the skill of the physician performing the ultrasound and his or her experience with features of TCS.

KEY TERMS

Coloboma—An abnormality on the upper or lower eyelid that often gives the lid a droopy appearance.

Craniofacial—Relating to or involving both the head and the face.

Tracheostomy—An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

Treatment and management

Newborn infants with severe TCS may require a ventilator, tracheostomy, or feeding tube if life-threatening breathing or feeding problems exist. A cleft palate can be repaired with surgery. Hearing aids can help individuals with hearing loss.

For most individuals, the problems of TCS are largely cosmetic. Plastic surgery can help to build the bone structure of the face, which may improve appearance as well as breathing and feeding. Surgeons can use bone grafts to build up the underdeveloped cheekbones. The jawbone can be "lengthened" and its angle repositioned. The bridge of the nose can be narrowed. Ears can be reconstructed using cartilage from the ribcage. Surgery can also be performed on the eye area.

This reconstruction may take multiple surgeries at different ages. Each individual must be evaluated for his or her unique features and needs. Surgeries are timed with facial growth and emotional needs and maturity of the patient.

Prognosis

A small percentage of newborns with TCS will have life-threatening breathing difficulties, and infant deaths can occur. However, the majority of individuals with TCS have a normal lifespan.

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FACES: The National Craniofacial Association. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

Treacher Collins Foundation. Box 683, Norwich, VT 05055. (800) 823-2055.

WEBSITE

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Amie Stanley, MS

Triose phosphate isomerase deficiency

Definition

Triose phosphate isomerase (TPI) deficiency is a rare non-sex-linked (autosomal) disorder that is a result of an insufficient amount of the enzyme triose phosphate isomerase. This disorder is inherited as a dominant trait and it is known to be caused by more than one different mutation in the same **gene** (allelic variants).

Description

Triose phosphate isomerase is an enzyme involved in the breakdown of glucose into the energy required to sustain cellular metabolism. Glucose is first converted into the chemical pyruvate. Pyruvate then enters the tricarboxylic acid cycle (TCA cycle) to produce ATP, the chemical form of energy used by the cells. Glucose is broken down to the chemical pyruvate via a chemical pathway that involves 10 enzymes. TPI is the fifth enzyme in this reaction chain. The two major products of the reaction proceeding the TPI reaction are D-glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP). These two chemicals are isomers, which means that they have the same chemical formulas but different chemical structures. TPI is the enzyme that converts DHAP into GAP. This conversion (isomerization) is important because it is only GAP that is used in the subsequent steps in the reaction pathway to the essential pyruvate molecules.

Under normal physiological conditions, DHAP is produced in much greater quantities than GAP (approximately 20:1). Therefore, it is essential that TPI convert the DHAP to GAP to increase the overall efficiency of pyruvate production from glucose. Individuals affected with TPI deficiency have extremely low levels of TPI activity because the enzyme that they do produce is not properly formed and, thus, it is highly inefficient.

Genetic profile

The gene that is responsible for the production of TPI has been localized to a region on chromosome 12. There are at least five mutations in this gene that lead to TPI deficiency. In every case, very slight changes in the chemical structure of TPI occur such that the TPI produced is less effective than a normal TPI molecule, especially when the body is hot, either from the weather or from exercise.

Demographics

TPI deficiency is extremely rare. In 1998, there were only 13 people known to be living with TPI deficiency, eleven children and two adult Hungarian brothers affected with an extremely mild form of the disease. Since 1998, at least five of these children have passed away. The documented rarity of this disorder does not seem to coincide with the observed frequency of reduced TPI activity in the population.

In a 1996 study of unselected individuals of Caucasian and Japanese descent, a Japanese researcher found that approximately five out of every 1,000 individuals had TPI activity that was only half of the normal TPI activity. In a separate study, it was estimated that nine in 1,713 Caucasians and seven in 168 African-Americans showed these low levels of TPI activity. One possible explanation is that complete TPI deficiency is an embryolethal condition. In other words, if complete TPI deficiency is inherited at conception, this embryo is miscarried before the mother even knows that conception had occurred.

All of the mutations in the gene responsible for the production of TPI are expressed as dominant traits. This means that a child can inherit this condition from just one of his or her parents. Also, if one child has been born affected with TPI deficiency, the likelihood that a second child, of the same parents, will also be affected is 50%. This likelihood is increased to 75% if both parents carry the defective gene.

Signs and symptoms

TPI deficiency affects primarily the circulatory and nervous systems. Disorders of the circulatory system include at least four separate forms of anemia (a lack of properly functioning red blood cells) that cause a lack of oxygen transport to the tissues and organs of the body. Disorders of the nervous system include developmental retardation and degenerative neurologic disorder with spasticity, a condition in which the nervous system progressively degenerates and the affected person suffers from spasticity similar to that seen in people with multiple sclerosis.

Because of the malformations of the red blood cells in TPI deficiency affected individuals, the liver, the organ that is responsible for cleaning the blood, often becomes overworked. This causes jaundice (an abnormal yellowing of the skin and the whites of the eyes). Heart failure is also quite common and is often the cause of death in TPI deficiency patients.

People affected with TPI deficiency are generally highly susceptible to recurrent infections. This tendency is believed to be due to a depression of the immune system caused by improper blood function.

Diagnosis

If a family history of the disease leads to suspicion, TPI deficiency can be detected prenatally by a test of umbilical cord blood. A device recognized by the U. S. Food and Drug Administration is available to measure the activity of TPI on red blood cells taken in a sample. This device provides a definitive test for TPI deficiency. A blood test indicating extremely elevated levels of DHAP is also indicative of TPI deficiency.

Another blood test that can be performed is an autohemolysis test. This test allows TPI deficiency to be differentially diagnosed from certain other enzymatic deficiencies. In this test, samples of blood are drawn and incubated at body temperature for 48 hours. After this time, the amount of breakdown of the red blood cells is recorded. One sample is left untreated, one sample has added glucose, and a third sample has added ATP. If the untreated sample shows higher than normal breakdown of the red blood cells, but those samples treated with glucose or ATP show a lessened breakdown of red blood cells, this is indicative of TPI deficiency. If glucose, but not ATP, slows the breakdown of the red blood cells, this indicates a diagnosis of G6PD deficiency. If ATP, but not glucose, slows the breakdown of the red blood cells, this indicates a diagnosis of **pyruvate kinase deficiency**. G6PD and pyruvate kinase are two other enzymes involved in the breakdown of glucose to pyruvate to ATP.

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Thermolabile—Heat-sensitive. A thermolabile protein is a protein that easily loses its shape when heated even only slightly.

Transversion—A genetic term referring to a specific substitution of one base pair for another. There are only four possible tranversions: guanine for cytosine, cytosine for guanine, adenine for thymine, or thymine for adenine.

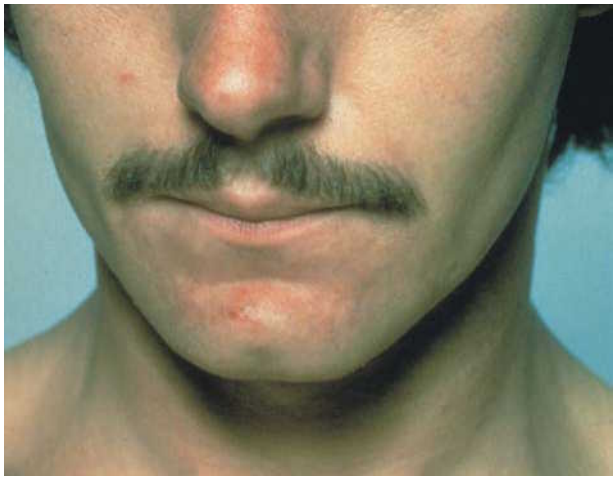
Triose phosphate isomerase—Abbreviated TPI, this is the enzyme responsible for the conversion of dihydroxyacetone phosphate (DHAP) into D-glyceraldehyde-3-phosphate (GAP). DHAP and GAP are the two major products of a step in the multi-step process that converts glucose into ATP to supply the body with the energy it needs to sustain itself. Only GAP can continue in this process, but DHAP is produced in much higher quantities. People with TPI deficiency cannot change DHAP into GAP as efficiently as unaffected people, resulting in insufficient amounts of ATP from glucose to maintain normal cell function.

Treatment and management

No treatment is currently available for TPI deficiency. Studies are ongoing to determine the feasibility of bone marrow transplants and enzyme replacement therapies. In 1999, TPI deficiency was corrected in a four-year-old boy by an enzyme replacement blood transfusion treatment. However, due to the temporary nature of the observed corrections in the biochemistry, it was concluded that a sustained reversal of the symptoms of TPI deficiency would require a continuous delivery of an active form of the TPI enzyme.

Prognosis

There are only two reported cases of TPI deficiency affected individuals living beyond the age of six. These



Malformations of the red blood cells in triose phosphate isomerase deficiency cause the liver, the organ responsible for cleaning the blood, to become overworked. This results in jaundice, an abnormal yellowing of the skin and the whites of the eyes. *(Custom Medical Stock Photo, Inc.)*

are a set of Hungarian brothers, one who did not develop neurological symptoms of TPI deficiency until 1980, at the age of 12, and an older brother, who was 30 in 2001, who has no neurological symptoms and suffers only from anemia. Enzyme replacement therapy and/or bone marrow transplantation may eventually prove to be effective means of treating TPI deficiency, and improve survival rates for this rare genetic disorder.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

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Paul A. Johnson

Trisomy *see* **Chromosomal abnormalities**

Trisomy 13 *see* **Patau syndrome**

Trisomy 18

Definition

Trisomy 18 is a genetic syndrome of multiple congenital anomalies and severe to profound mental retardation. It is caused by the presence of an extra chromosome 18 in some or all of the cells of the body. Babies with the condition usually do not survive past several months of age. Trisomy 18 in the embryo/fetus is also a common chromosomal cause of pregnancy loss.

Description

Chromosomes are the microscopic structures inside cells that carry the **genes**. The genetic material inside each cell contains all of the instructions the body needs to develop and function normally. Humans have 23 different pairs of chromosomes. Chromosomes 1-22 are numbered from largest to smallest, and as a group are known as the autosomes. The last pair of chromosomes are designated X and Y, and are known as the sex chromosomes—females have two X chromosomes and males have one X and one Y. Other than sperm and eggs, each cell in the body normally has 46 chromosomes—a pair of each of the autosomes plus two sex chromosomes. In order for normal development and functioning to occur, chromosomes and genes must be present in the correct quantity and in the correct proportion to each other. Too much or too little genetic material usually causes serious problems.

The term euploid means "good set," and is used to designate a full set of 46 chromosomes. A cell is aneuploid ("not a good set") if it has any number of chromosomes other than 46. A trisomy is one type of aneuploidy, and refers to a cell that contains three of the same chromosome. Trisomy 18, then, refers to three chromosomes 18. After **Down syndrome** (trisomy 21), trisomy 18 is the most common autosomal aneuploid condition seen in

live-born babies. Trisomy 18 is also known as Edwards syndrome.

Edwards syndrome is comprised of a specific but broad pattern of multiple congenital anomalies and mental retardation. Babies with Edwards syndrome tend to have similar physical features and medical problems because they all have the same genetic imbalance—an extra copy of the genes on chromosome 18. The physical anomalies associated with Edwards syndrome involve nearly every organ and system of the body. However, some anomalies occur more often than others, such as those of the heart, kidney, brain, skeleton, and craniofacial (head and face) area. The birth defects are typically serious and, combined with the large number of anomalies possible, result in a high mortality rate. About 60% of newborns with Edwards syndrome die within the first week, and 80% do not survive past one month of age. Even those with Edwards syndrome who live longer will have severe to profound mental retardation and chronic medical problems, necessitating involved care and monitoring throughout their lives.

KEY TERMS

Aneuploidy—An abnormal number of chromosomes in a cell. Trisomy 18 and trisomy 13 are examples of aneuploid conditions.

Chromosome translocation—The exchange of genetic material between chromosomes, which can lead to extra or missing genetic material.

Geneticist—A specialist (M.D. or Ph.D.) who has training and certification in diagnosing, managing, and counseling individuals/families with genetic disorders. Genetics counselors hold a master's degree in medical genetics, and provide many of the same services as geneticists.

Meiosis—The process in which a cell in the testes or ovaries undergoes chromosome separation and cell division to produce sperm or eggs.

Mitosis—The process by which a somatic cell—a cell not destined to become a sperm or egg—duplicates its chromosomes and divides to produce two new cells.

Mosaicism—A genetic condition resulting from a mutation, crossing over, or nondisjunction of chromosomes during cell division, causing a variation in the number of chromosomes in the cells.

Neonatologist—A physician (pediatrician) who has special training in the care of newborns (neonates).

Nondisjunction—Non-separation of a chromosome pair, during either meiosis or mitosis.

Perinatologist—A physician (obstetrician) who has special training in managing difficult pregnancies. Some prenatal tests, such as chorionic villus sampling and level II ultrasound, are performed primarily by perinatologists.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

Genetic profile

Edwards syndrome occurs in three different forms: full trisomy 18, mosaic trisomy 18, and partial trisomy 18. Before each of these is described, however, it is helpful to review the basics of normal reproduction and early embryonic development. As noted, cells in the body normally contain 46 chromosomes in 23 pairs, except sperm in males and eggs in females, which contain one chromosome of each pair, or 23 total. Meiosis is the process by which sperm and eggs, collectively known as gametes, are produced. In normal meiosis, the 46 chromosomes line up in pairs in the middle of a cell, and the cell divides down the middle separating each pair of chromosomes. When a sperm fertilizes an egg at conception, the 23 chromosomes from each gamete combine. A process of repeated chromosome duplication followed by cell division, known as mitosis, then begins. A cell that goes through mitosis produces two new cells, each with 46 chromosomes. A developing human is called an embryo during the eight weeks after conception, and a fetus for the remainder of pregnancy.

Full trisomy 18

Occasionally, chromosomes of a single pair do not separate during meiosis, an abnormal process known as nondisjunction. The result is one gamete with 24 chromosomes and another with 22. If a gamete with 24 chromosomes results in conception with a normal counterpart, an embryo with 47 chromosomes is produced. In most cases, all cells in the body will then have 47 chromosomes, a condition known as full trisomy 18 (when referring to an individual with the disorder, unless otherwise specified, the term "trisomy 18" implies a full trisomy, whereas Edwards syndrome may refer to any of the forms).

Nondisjunction of two chromosomes 18 during the formation of an egg or sperm is by far the most common cause of Edwards syndrome. Nondisjunction is a chance occurrence, with no known causative or preventive factors. The incidence of nondisjunction does increase,

however, as men and women age. For anyone who has a fetus or child diagnosed with trisomy 18, the risk for a chromosomal disorder of any type in subsequent offspring is about 1%, the exception being women over age 35, who face their age-related risk.

Mosaic trisomy 18

If the body contains a mixture of cells, some with trisomy 18 and some with a normal chromosome count, the condition is called mosaic trisomy 18. A small percentage of Edwards syndrome cases are due to mosaic trisomy 18.

Mosaic trisomy 18 occurs in one of two ways. The first involves mitotic (rather than meiotic) nondisjunction of chromosomes 18, in which a cell undergoing mitosis in a chromosomally normal embryo produces one cell with trisomy 18 and another with monosomy 18. The cell with monosomy 18 cannot survive, but if the trisomic cell survives, all cells in the body derived from it will have trisomy 18. These trisomic cells, combined with the normal cells that continue to develop, result in mosaic trisomy 18. The other cause of mosaicism involves an embryo with full trisomy 18. In this case, however, one cell loses its extra chromosome during mitosis. The result is a euploid cell, which in turn produces a euploid cell line in addition to the original trisomic cell line. Since mitotic nondisjunction appears to be the cause in most cases, and is due purely to chance, the recurrence risk for subsequent offspring after the diagnosis of mosaic trisomy 18 is less than 1%.

Because they have some normal cells, individuals with mosaic trisomy 18 tend to be less severely affected than those with full trisomy 18, but not always. Much of the prognosis depends on the total percentage of trisomic cells in the body and/or the proportion of trisomic cells in specific tissues and organs. There is no way to determine exact percentages of cells, and therefore no way to provide an accurate prognosis.

Partial trisomy 18

A third cause of Edwards syndrome is a rearrangement, or translocation, of genetic material between chromosome 18 and another chromosome. An unbalanced chromosome translocation (extra and/or missing genetic material) may result in an embryo that has an extra piece of chromosome 18, known as partial trisomy 18. If cells are trisomic for a portion of chromosome 18, the result could be a form of Edwards syndrome. However, translocations between chromosomes can be complicated, and some cases of partial trisomy 18 may result in a pattern of anomalies that does not resemble Edwards syndrome.

Unbalanced translocations can occur in an embryo for the first time (*de novo*), or they can be inherited from a healthy parent who is a carrier of the translocation in a balanced state (no missing or extra genetic material). Normal blood chromosome tests on both parents implies the translocation was *de novo*, which means no increased risk for subsequent offspring. Detection of a balanced translocation in one parent, however, presents an increased risk for unbalanced translocations in subsequent offspring, as well as an increased risk for pregnancy loss. In cases of partial trisomy 18, **genetic counseling** is critical to help determine risks and available options. Chromosome translocations resulting in partial trisomy 18 make up a small percentage of Edwards syndrome cases.

Demographics

The incidence of Edwards syndrome is about one in 5,000 births. Two-thirds of all newborns with the condition are female, probably because males with trisomy 18 are more likely to be miscarried. The condition is not known to occur more frequently in any ethnic group or in any part of the world. Increased parental age is the only factor known to result in a greater risk for trisomy 18. In the United States, parents of babies with trisomy 18 average about 32 years of age, while 26 is the average age for parents of children without a chromosomal disorder. The risk increases with age in both sexes, but begins earlier and is more pronounced in women.

Increasing maternal age elevates the risk for chromosomal disorders due to nondisjunction in general, not just trisomy 18. For instance, a 20-year-old woman has about a 1 in 10,000 chance of having a child with trisomy 18, while the risk of having a child with *any* chromosomal disorder at that age is 1 in 800. By age 35, those same risks have risen to 1 in 2,000 and 1 in 200 respectively, and increase to 1 in 600 and 1 in 65 at age 40. Other common chromosomal disorders caused by nondisjunction that result in live birth include trisomy 21 (Down syndrome), trisomy 13 (**Patau syndrome**), and several conditions caused by aneuploidy of the sex chromosomes.

Signs and symptoms

Many physical anomalies and medical complications are associated with Edwards syndrome. In fact, well over 100 different anomalies have been reported in the medical literature. The more common findings are categorized and described below.

Prenatal anomalies

The majority of pregnancies in which the embryo/fetus has trisomy 18 will result in miscarriage or

stillbirth. Some physical anomalies of the heart, skeleton, brain, kidneys, and body walls have the best chance of being detected by prenatal ultrasound. Other, pregnancy-related findings include intrauterine growth restriction (IUGR) of the fetus, a single umbilical artery (also called two vessel cord), and too much (polyhydramnios) or too little (oligohydramnios) amniotic fluid. While detection of fetal anomalies by ultrasound may lead to suspicion of Edwards syndrome, the diagnosis can only be confirmed by chromosome testing. Women carrying a fetus with Edwards syndrome sometimes report they feel little movement. Cesarean sections are more common due to abnormal fetal position or fetal distress near term.

General anomalies

Of those babies with Edwards syndrome that are live-born, two-thirds are delivered several weeks earlier or later than their expected due date. Low birth weight is common, as are low Apgar scores (measurements of a newborn's activity just after birth). Newborns are frail, and tend to have a weak cry and difficulty feeding. Muscles may be poorly developed, and often become tight and contracted (hypertonic). Extra hair (hirsutism) on the forehead and back is sometimes seen, as is loose, redundant skin.

Abnormalities of the lungs, kidneys, pancreas, spleen, and gastrointestinal system are associated with Edwards syndrome. The thyroid, thymus, and adrenal glands may be affected. Anomalies of the breastbone, radius (bone in the forearm), ribs, pelvis, and the spine (**scoliosis**) are the more frequent skeletal findings. An abdominal wall defect (**omphalocele**) or hernia in the abdominal region may be present. Genital (sex organ) anomalies in both males and females have been described.

Heart anomalies

Ninety percent of babies with Edwards syndrome have one or more heart defects. Ventricular septal defects (VSD) and atrial septal defects (ASD), holes between the lower and upper chambers of the heart respectively, are the most common cardiac problems. Patent ductus arteriosis (open connection between the pulmonary artery and aorta) and abnormal heart valves are also typical.

Craniofacial anomalies

Small head size (microcephaly) and a prominent occiput (back of the skull) are variations in skull shape typical of Edwards syndrome. Common facial features include widely spaced and/or slanted eyes, skin folds at the inner eyelid (epicanthal folds), ptosis (drooping) of the eyelids, low-set malformed ears, a small oral opening, narrow palate or cleft lip/palate, and a small jaw (micrognathia).

Hand and foot anomalies

A specific pattern of hand and foot anomalies is seen in most infants with Edwards syndrome. Clenched hands, with the index finger overlapping the third and the fifth finger overlapping the fourth, are a classic sign. Abnormal dermatoglyphics (finger print pattern), underdeveloped nails, outward or inward deviation of the hand, underdeveloped or absent thumbs, and a single crease across the palm are other frequent anomalies of the hands. Abnormalities affecting the feet include so-called "rocker-bottom feet" and **clubfoot**.

Central nervous system anomalies

Probably the most medically significant abnormal development that occurs in Edwards syndrome involves the brain. Some anomalies, such as a small cerebellum or **hydrocephalus** (increased fluid within the brain), can be visualized by ultrasound or other imaging techniques. However, some neurologic problems may only be noticed through their physical effects. For example, difficulties in feeding and breathing, hypertonic muscles, a diminished response to sound, seizures, and severe mental retardation all indicate serious neurologic deficits. **Spina bifida** (open spine) is an infrequent but serious problem affecting the spinal cord. Babies with spina bifida usually have some degree of paralysis below the point on the back where the spine failed to close.

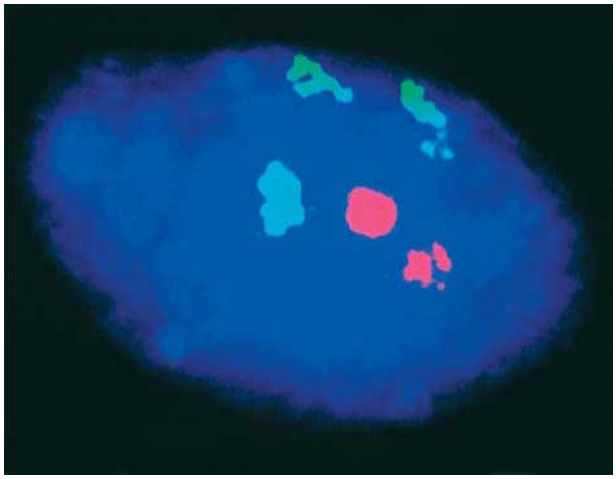
Diagnosis

Prenatal

Two screening and two diagnostic procedures for trisomy 18 are available to women during pregnancy. Following are brief explanations of each of the prenatal testing alternatives.

Maternal serum alpha-fetoprotein (MSAFP)-Plus, also known as the "triple screen," is a routine maternal blood test offered to women at 15-20 weeks of pregnancy. It screens for open defects (such as spina bifida), Down syndrome, and trisomy 18. However, the screen's sensitivity for trisomy 18 is not as well established as it is for the other conditions. Test results provide a risk adjustment only, not a diagnosis of any condition in the fetus. Any woman who has a result showing an increased risk for trisomy 18 in the fetus is offered follow-up testing such as **amniocentesis** or a detailed (level II) ultrasound.

Ultrasound, also called sonography, visualizes structures inside the body using high frequency sound waves.



FISH (Fluorescent In Situ Hybridization) micrograph of Trisomy 18 chromosomes (green) in the nucleus of a cell (blue). In this image, the three copies of chromosome 18 are visible. *(Photo Researchers, Inc.)*

During a prenatal ultrasound, a technician or doctor moves an instrument (transducer) back and forth across the skin of a pregnant woman's lower abdomen. The transducer emits and receives harmless high frequency sound waves, which the ultrasound machine then converts into images of the fetus. Today's sophisticated ultrasound machines, used by skilled technicians and doctors, can detect a number of different physical anomalies in the fetus. An ultrasound screen for trisomy 18 has good (but not absolute) sensitivity, and presents no risk to the mother or fetus. Ultrasound becomes more sensitive for trisomy 18 the later in pregnancy it is performed. A level II ultrasound is performed after 20 weeks of pregnancy by a specialist (perinatologist). An abnormal ultrasound suggesting trisomy 18 would lead to the option of amniocentesis to confirm the diagnosis.

Chorionic villus sampling (CVS) is a method used to obtain tissue (chorionic villi) from the edge of the developing placenta. CVS is typically performed at 10-12 weeks of pregnancy. Chorionic villi come from the fetal side of the placenta, and thus are chromosomally the same as cells in the fetus. Guided by ultrasound, a physician inserts a needle through either the abdomen or the cervix, into the placenta, and removes a small sample of tissue. Cells from the sample are analyzed under the microscope and a chromosome count is obtained. CVS carries a risk for miscarriage of approximately 1 in 150, and appears to have a very small risk of causing certain types of limb defects in the fetus as well. In about 3% of cases, CVS produces results that are difficult to interpret, which may lead to a follow-up amniocentesis.

Amniocentesis is the most widely used procedure to obtain fetal cells for **genetic testing**. The procedure can be performed anytime after about 15 weeks of pregnancy. Under ultrasound guidance, a physician passes a thin needle through the lower abdomen into the amniotic sac and removes a small amount of amniotic fluid. Fetal skin cells that normally float in the fluid are then extracted for genetic analysis. Diagnosis of chromosomal disorders by this method is highly accurate. Amniocentesis causes a miscarriage in about 1 in 300 women who have the procedure, but poses no other serious risk to the fetus.

The benefit of CVS and amniocentesis is their accuracy at detecting trisomy 18, while the drawback is their risk to the pregnancy. The procedures are typically not offered unless the risk for a chromosomal disorder in the fetus is greater than the risk of the procedure, such as in pregnant women who are 35 or older, a couple with a previous child with trisomy 18, and any woman who carries, or whose partner carries, a balanced chromosome translocation. Detection of fetal anomalies by ultrasound or an abnormal MSAFP-Plus screen would lead to the option of amniocentesis.

The benefit of ultrasound and MSAFP-Plus is their lack of risk to the pregnancy, while the drawback is that neither procedure is diagnostic. Women who wish to first modify their risk for a fetal chromosomal disorder (and spina bifida) may choose screening. In any case, prenatal testing, whether screening or diagnostic, is never mandatory. Careful consideration must always be given to what action might be taken after an abnormal result, and how reassuring a normal result might be.

Postnatal

A newborn with typical signs of Edwards syndrome can sometimes be diagnosed from a physical examination alone, especially by a physician who is familiar with the condition such as a geneticist or neonatologist. However, chromosome testing is the only method to confirm the diagnosis, and should always be performed if Edwards syndrome is suspected. Chromosome analysis helps to determine whether the underlying cause is full, mosaic, or partial trisomy 18, and may exclude other syndromes with similar signs and symptoms. Fetuses and newborns with Edwards syndrome sometimes die before chromosome analysis can be performed. In those cases, the diagnosis unfortunately cannot be confirmed, and an accurate cause and recurrence risk cannot be given.

Chromosome testing will detect full trisomy 18 with near 100% accuracy. Likewise, a translocation of chromosome 18 that produces signs of Edwards syn-

drome should be detected in virtually every case. Mosaic trisomy 18 presents more of a problem for chromosome analysis. The likelihood of confirming mosaic trisomy 18 depends on the percentage of trisomic cells in the particular tissue examined. Mosaicism, if present, can be confirmed by chromosome testing, and usually is. However, normal chromosome tests do not rule out the possibility of trisomic cells elsewhere in the body.

Treatment and management

Medical management of an infant with Edwards syndrome depends on the number and severity of anomalies present. In order to make the best-informed and most appropriate decisions for their child, parents must establish a close working relationship with the treating physicians.

Regardless of the medical procedures that might be performed, most babies with Edwards syndrome will not survive. Nearly all will be transferred to the neonatal intensive care unit (NICU) after birth. In some cases, parents elect not to have any life-prolonging, heroic measures taken should their child experience cardiac or respiratory failure. They may also elect not to have certain types of surgery performed if other complicating medical problems make it unwise.

A more medically stable, less severely affected infant with Edwards syndrome will likely require various medical procedures and treatments. Surgical repair of certain physical anomalies, ventilator (breathing) support, medications, and/or placement of a feeding tube into the stomach are common. A baby may go home and remain there after some length of hospital stay, or may need to be readmitted one or more times. For those children that show some possibility of longer-term survival (more than six months), a plan for their medical care, both in the hospital and at home, must be established. Parents should also be informed of the various educational and support services available to them, including the Support Organization For Trisomy 18, 13, and Related Disorders (S.O.F.T.). Genetic counseling, to discuss the cause, prognosis, and recurrence risks for their child's type of trisomy 18, can be of great help to parents.

There is no way to prevent the occurrence of trisomy 18. The technology now exists to test multiple embryos conceived by in vitro fertilization for certain chromosome anomalies, but this is very expensive and is only performed at several centers in the world.

Prognosis

The prognosis for a baby born with trisomy 18 is poor. On average, about 40% of newborns with trisomy 18 survive the first week, 20% are alive at one month, 6% at six months, and about 5% live past their first birthday. Survival rates are somewhat higher for children with mosaic or partial trisomy 18. As is the case before birth, males with trisomy 18 have a higher mortality rate than females, with about one-third as many males as females surviving infancy.

The outlook for trisomy 18 is not likely to change much in the coming years. Surgery to repair various birth defects has improved dramatically over the years. However, most babies with trisomy 18 do not die from repairable anomalies. For those parents whose babies are expected to survive some length of time, connecting them with support groups and providing them with accurate information as soon as possible is important.

Resources

PERIODICALS

Baty, Bonnie J., Brent L. Blackburn, and John C. Carey. "Natural History of Trisomy 18 and Trisomy 13: I. Growth, Physical Assessment, Medical Histories, Survival, and Recurrence Risk." *American Journal of Medical Genetics* 49 (1994): 175-88.

Baty, Bonnie J., Brent L. Blackburn, and John C. Carey. "Natural History of Trisomy 18 and Trisomy 13: II. Psychomotor Development." *American Journal of Medical Genetics* 49 (1994): 189-94.

Matthews, Anne L. "Chromosomal Abnormalities: Trisomy 18, Trisomy 13, Deletions, and Microdeletions." *Journal of Perinatal and Neonatal Nursing* 13 (1999): 59-75.

ORGANIZATIONS

Chromosome 18 Registry and Research Society. 6302 Fox Head, San Antonio, TX 78247. (210) 567-4968. <http://www.chromosome18.org>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. <http://www.nsgc.org/GeneticCounselingYou.asp>.

Support Organization for Trisomy 18, 13 and Related Disorders (SOFT). 2982 South Union St., Rochester, NY 14624. (800) 716-SOFT. <http://www.trisomy.org>.

Scott J. Polzin, MS, CGC

Trisomy 21 *see* **Down syndrome**

Tuberous sclerosis complex

Definition

Tuberous sclerosis complex (TSC) is a genetic condition that affects many organ systems including the brain, skin, heart, kidneys, eyes, and lungs. Benign (noncancerous) growths or tumors called hamartomas form in various parts of the body, disrupting their normal functions.

Description

The term tuberous sclerosis refers to the small, knoblike growths in the brain of patients with TSC that were found in patients upon autopsy and, today, can be viewed using computed tomography (also called a CT scan). The condition is also referred to as tuberose sclerosis or simply tuberous sclerosis. The designation tuberous sclerosis complex is used to distinguish this condition from another genetic condition called **Tourette syndrome** that is abbreviated TS.

Persons with TSC have a variety of symptoms ranging from very mild to severe. Affected individuals may experience no serious health problems and, in the absence of a thorough clinical examination, may go through life without knowing that they are affected. Conversely, patients with TSC may have problems with behavioral, mental, and emotional functions as well as with their kidneys, heart, and eyes. In addition, specific skin abnormalities, often medically insignificant, are among the most common symptoms of TSC.

Genetic profile

TSC is an autosomal dominant genetic disorder caused by a single change or alteration in a **gene** called a mutation in either the TSC1 gene, located on chromosome 9, or the TSC2 gene, located on chromosome 16. Approximately two-thirds (66%) of patients with TSC have it as the result of a new change in one of the TSC genes; that is, it was not inherited from one of their parents. When a new change occurs, it most commonly occurs in the TSC2 gene. An individual must have a mutation in one of these two copies of a TSC-causing gene in order to develop the condition. In addition, a person who has been diagnosed with TSC and who, therefore, has a genetic mutation in one of the TSC genes, has a 50% chance of passing on the genetic mutation to his or her offspring. Laboratory testing for changes in the TSC genes is not currently available.

TSC is a condition that can be caused by a change in either one of two separate genes. In addition, people who have the same change in the same gene may have very different medical problems and symptoms.

TSC1 is responsible for producing the protein hamartin and TSC2, tuberin. Both genes are known as tumor suppressor genes meaning that their normal function is to prevent the growth of tumors. Conversely, when gene function is altered, tumor growth results. Research on how the disruption of either protein results in the clinical condition of TSC is ongoing.

It is currently believed that every person who inherits or develops a mutation in either the TSC1 or TSC2 gene will develop some form of TSC. However, the severity of the disease, with its wide range of symptoms and complications, cannot accurately be predicted by identifying the specific **gene mutation**.

Germline mosaicism can explain the rare occurrence of unaffected parents having more than one child with TSC. Germline refers to the gonadal cells (sperm in males and eggs in females) and mosaicism refers to the presence of different cell lines in any given individual. A person with germline mosaicism for either the TSC1 or TSC2 gene is not affected with TSC but may have an affected child. Unaffected parents of a child with TSC are quoted a 2-3% chance of having additional affected children. Typical **genetic testing** methods are performed on somatic (non-germline) tissues such as blood or skin and, therefore, will not detect germline mosaicism.

Demographics

Although tuberous sclerosis complex is considered to be a rare condition, estimates of the prevalence of the disorder have increased as clinical testing methods have improved. In the United States, as many as one child in 6,000 born is affected with TSC and about 50,000 people are currently living in the U.S. with the disease. TSC is seen in all ethnic groups and populations and, worldwide, there are between one and two million cases.

Signs and symptoms

The basic underlying cause for illness and, less often, death due to tuberous sclerosis complex is the development of growths called hamartomas throughout the body. Hamartoma is a general term used to describe tumor-like growths that are not cancerous and are composed of cells usually found in that site but poorly developed. While these growths are typically benign (i.e., not cancerous), their presence often disrupts the normal functions of a particular organ system. The various hamartomas found in TSC patients can be further distinguished and classified by their location and their histo-

KEY TERMS

Bone cysts—Fluid- or air-filled space within the bones.

Cardiac rhabdomyoma—Benign (non-cancerous) tumor of the heart muscle.

Cerebral white matter migration lines—Pattern of defects found in the cerebral cortex of the brain probably caused by abnormal migration of neurons during brain formation.

Confetti skin lesions—Numerous light or white spots seen on the skin that resemble confetti.

Cortical tuber—Round (nodular) growth found in the cortex of the brain.

Dental pits—Small, shallow holes or crevices in the tooth enamel.

Facial angiofibromas—Benign (non-cancerous) tumors of the face.

Forehead plaque—Flat, fibrous skin growth on the forehead.

Gingival fibromas—Fibrous growths found on the gums.

Hamartomatous rectal polyps—Benign (non-cancerous) growths found in the rectum.

Hypomelanotic macules—Patches of skin lighter than the surrounding skin.

Lymphangiomyomatosis—Serious lung disease characterized by the overgrowth of an unusual type of muscle cell resulting in the blockage of air, blood, and lymph vessels to and from the lungs.

Nonrenal hamartoma—Benign (non-cancerous) tumor-like growths not found in the kidneys that often disrupt the normal function of a particular organ system.

Nontraumatic ungual or periungual fibroma—Fibrous growth that appears around the fingernails and/or toenails

Renal angiomyolipoma—Benign (non-cancerous) tumors in the kidney that are made up of vascular tissue (angio), smooth muscle (myo), and fat (lipoma).

Renal cysts—Fluid- or air-filled spaces within the kidneys.

Retinal achromic patch—Defect in the coloration of the retina.

Retinal hamartomas—Benign (non-cancerous) tumor found on the retina.

Shagreen patch—Area of tough and dimpled skin.

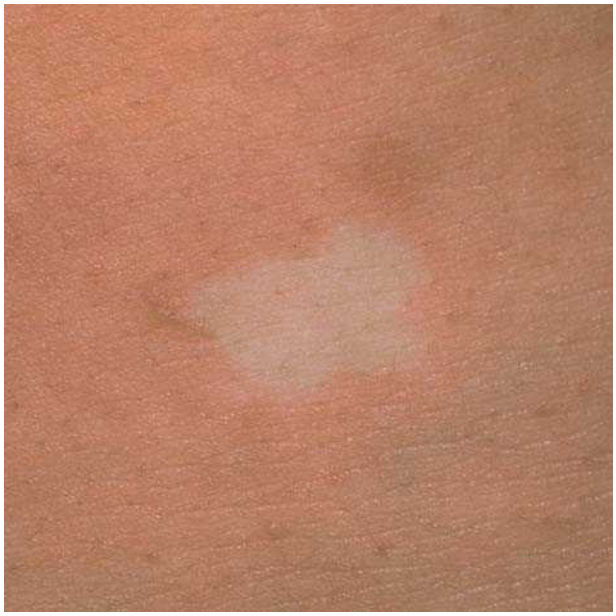
Subependymal giant cell astrocytoma—Benign (non-cancerous) tumor of the brain comprised of star-shaped cells (astrocytes).

Subependymal nodule—Growth found underneath the lining of the ventricles in the brain.

logical properties—that is, their physical composition and characteristic appearance under a microscope. As each hamartoma is comprised of different cellular elements, each one has a particular name. For example, while both are hamartomas, a fibroma is comprised of connective tissue whereas a lipoma is made up of fat cells.

While the organs affected vary from person to person, most people with TSC have some type of skin irregularities called lesions. Some of the most commonly seen skin lesions are hypomelanotic macules—white or light patches sometimes in an ash-leaf shape and called Ash-leaf spots. Many people in the general population have one or two light areas of skin. However, the presence of three or more such macules in any one individual is considered a major diagnostic finding of TSC. A second major diagnostic feature of the condition is the appearance of small, red bumps called fibromas, either on the face (facial angiofibromas) or around or under the finger- or toenails (ungual fibromas). In addition, rough patches of skin termed Shagreen patches are highly specific to a diagnosis of TSC. Finally, groups of small light circles called Confetti spots are considered a minor feature of the disorder.

In contrast to skin lesions, brain lesions tend to be serious and are responsible for the neurological symptoms and cognitive impairment seen in severely affected individuals. There are four primary abnormalities that can be detected by magnetic resonance imaging (MRI) or computer tomography (CT) scanning, the first of which are cortical tubers—nodular growths found in the cortex of the brain—and give tuberous sclerosis (literally “hard growths”) its name. Subependymal nodules are growths found underneath the lining of the ventricles in the brain and may cause no problems for the patient unless they grow or begin to block the flow of the cerebral spinal



A common sign of tuberous sclerosis is skin lesions called hypomelanotic macules. These are white or light patches of skin sometimes in an ash-leaf shape and called Ash-leaf spots. *(Custom Medical Stock Photo, Inc.)*

fluid. In contrast, subependymal giant cell astrocytomas, non-cancerous brain tumors comprised of star-shaped cells and found in about 5% of patients with TSC, can, if untreated, result in blindness, **hydrocephalus** (fluid on the brain), and even death. Finally, cerebral white matter migration lines may be seen through radiographic (x ray) studies and are considered a minor diagnostic feature of TSC.

About 85% of affected individuals will develop epileptic seizures at some point in their lifetime, most beginning by the first year of life. Research suggests that early control of **epilepsy** by medication will decrease the chance of a child developing serious mental complications. People with TSC have a range of mental abilities from normal to mild or moderate developmental delays and learning disabilities, to severe mental retardation. **Autism**, **attention deficit hyperactivity disorder (ADHD)**, and other behavioral problems are seen in affected individuals.

Fatty kidney tumors, known as renal angiomyolipomas, are one of the most common findings in TSC patients, affecting 70-80% of older children and adults, and often cause serious renal malfunction. In addition, the presence of multiple renal cysts (fluid filled areas within the kidneys) is suggestive of the condition. In addition to these benign growths, malignant kidney tumors may also develop.

The most common cardiac symptom is one or more tumors (cardiac rhabdomyomas) in the heart. These tumors are almost exclusively seen in infants and young children and usually spontaneously disappear by late childhood, thereby avoiding the need for surgery. About 47-67% of infants and children with TSC have heart tumors and some females develop the rhabdomyomas when they reach puberty.

Tuberous sclerosis complex affects the eyes in the form of retinal nodular hamartomas—multiple growths on the retina. A discoloration on the retina (retinal achromic patch) is also considered a minor feature of the condition.

In addition to the above, symptoms of TSC may include dental pits in the teeth, growths in the rectum (hamartomatous rectal polyps), bone cysts, growths on the gums (gingival fibromas) and other non-specific growths (nonrenal hamartomas). Women with TSC may develop lymphangiomyomatosis, a serious lung disease. Furthermore, all individuals with TSC are at a higher risk over the general population for developing specific cancers, with 2% of patients developing a malignant tumor in one of the affected body tissues such as kidney or brain.

Diagnosis

When a person exhibits signs of TSC or has a family history of the condition, an evaluation by a medical geneticist, neurologist, or other qualified professional is recommended to confirm (or rule out) the diagnosis and to recommend screening and management options for the individual. In addition, speaking with a genetic counselor may help families understand the genetics behind the disorder, their recurrence risks (chances for having another affected family member) and the practical and psychosocial implications of the disease on their personal situation.

Detection of hypomelanotic macules (light patches on the skin) can be performed quickly and easily using a special ultraviolet lamp called a Wood's lamp. This light emphasizes the lightened areas on the skin that may otherwise be difficult to see using normal light. Other skin lesions called fibromas are easily visible and identifiable due to their characteristic smooth form, red color, and their even distribution on the face and/or their protrusions among the nails on the fingers and toes. Radiographic imaging using ultrasound, MRI, or CT technology can detect growths present in the brain, kidneys, heart, and eyes.

As basic understanding of and testing methods for tuberous sclerosis complex have improved, criteria used for confirming a diagnosis of tuberous sclerosis complex have been revised. The National Institutes of Health

(NIH) held a consensus conference on TSC in 1998 and published the following diagnostic criteria in 2000:

Major features:

- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual fibroma
- Hypomelanotic macules (more than three)
- Shagreen patch
- Multiple retinal hamartomas
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma (one or more)
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor features:

- Multiple randomly distributed dental pits
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- Confetti skin lesions
- Multiple renal cysts

A confirmed diagnosis of TSC requires that a patient display either two major features or one major and two minor features, a suspected diagnosis one major and one minor feature, and a possible diagnosis one major or two minor features in any one individual.

Treatment and management

Optimal treatment for TSC is dependent upon proper disease management. The following should be performed on all patients with TSC at the time of diagnosis to confirm a diagnosis of the disease as well as obtain baseline medical data for future evaluations:

- dermatologic (skin) examination
- fundoscopic (eye) examination
- renal (kidney) imaging study
- cardiac electrocardiogram (ECG) and echocardiogram (ECHO)
- brain magnetic resonance imaging (MRI)

Since the characteristic feature of tuberous sclerosis complex is the growth of benign tumors, treatments are often focused on appropriate surgical interventions to arrest tumor growth or remove tumors whose growth has resulted in or may lead to medical complications especially in the kidney or brain. Regular brain MRI studies should be performed in children and adults with previous findings as clinically indicated and every one to three years in children and, less frequently, in adults without symptoms. In addition, periodic brain electroencephalogram (EEG) studies are recommended for both children and adult patients when clinically indicated.

Children without previous kidney findings should be offered renal imaging studies using ultrasound, MRI, or CT scanning every three years until they reach adolescence and then, every one to three years as adults. Likewise, asymptomatic adults should have imaging of their kidneys every one to three years. Both children and adults who have kidney symptoms should be monitored using imaging studies every six months to one year until the tumor growth stabilizes or decreases.

Any child with cardiac rhabdomyomas should be monitored every six months to one year until the tumor stabilizes or regresses completely. Adults with previous findings of cardiac tumors should be monitored as clinically recommended by their treating physician. While monitoring is important, cardiac rhabdomyomas, as well as retinal lesions and gingival fibromas, usually do not require treatment. In contrast to these benign tumors, cancerous tumors that develop in patients with TSC should be treated by an oncologist as appropriate.

Facial angiofibromas and peri- and subungual fibromas on the nails are common symptoms in TSC patients. While they are generally not medically significant, they can cause skin irritations or be a cosmetic concern to the individual. Special techniques involving dermabrasion or laser therapy can be performed by a dermatologist or plastic surgeon to remove such growths.

Patients with seizure disorders are prescribed specific medications to control seizures. As of 2001, a new anti-epileptic drug (vigabatrin) has been shown to be an effective medication in infants with seizures and has been shown to improve long-term outcomes in behavioral and intellectual areas. In addition to controlling seizures, early intervention programs that include special education, behavior modification, physical and occupational therapies, and speech therapy is often recommended for individuals with learning disabilities, developmental delays, mental retardation, autism, and other mental and emotional disorders.

Neurodevelopmental testing is appropriate at the time of diagnosis for all children and should be performed every three years until adolescence and for any adult diagnosed with TSC who displays signs of impairment. Subsequent evaluations should be done on both children and adults with previous findings of developmental delays or problems.

While present in only 1% of patients with TSC, almost exclusively in females, lung complications can be serious and even fatal. Symptoms may include spontaneous pneumothorax (air in the chest cavity), dyspnea (difficult breathing), cough, hemoptysis (spitting of blood), and pulmonary failure. Therefore, a computed tomography (CT) scan of the lungs is recommended for any TSC patient who has symptoms of lung disease or complications and for all female TSC patients at the age of 18. Clinical trials involving Tamoxifen and progesterone treatments have shown positive results in some patients with lung disease.

Prognosis

The lifespan of individuals with TSC varies with the severity of the condition in any one person. Many affected people have normal life expectancies and a high quality of life, relatively free of symptoms or complication of the disease. Conversely, severely affected or disabled individuals may experience a shortened lifespan and a high rate of illness and medical complications. Therefore, proper disease management, diagnostic monitoring, and follow-up are critical to achieving and maintaining optimal health in patients with TSC.

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ORGANIZATIONS

Tuberous Sclerosis Alliance. 801 Roeder Rd., Suite 750, Silver Spring, MD 20910. (800) 225-6872. <http://www.tsalliance.org>.

WEBSITES

Australasian Tuberous Sclerosis Society. <http://www.netspace.net.au/~atss/>.

The Global Tuberous Sclerosis Information Link. <http://members.aol.com/gtsil/ts/index.htm>.

Tuberous Sclerosis Alliance. <http://www.tsalliance.org>.

The Tuberous Sclerosis Association. <http://www.tuberous-sclerosis.org/>.

Pamela E. Cohen, MS, CGC

Turcot syndrome *see* **Familial adenomatous polyposis**

Turner syndrome

Definition

Turner syndrome is a chromosomal disorder affecting females wherein one of the two X-chromosomes is defective or completely absent.

Description

Chromosomes are structures in the nucleus of every cell in the human body. Chromosomes contain the genetic information necessary to direct the growth and normal functioning of all cells and systems of the body. A normal individual has a total of 46 chromosomes in each cell, two of which are responsible for determining gender. Normally, females have two X chromosomes and males have one X and one Y chromosome.

In Turner syndrome, an error occurring very early in development results in an abnormal number and arrangement of chromosomes. Most commonly, an individual with Turner syndrome will be born with 45 chromosomes in each cell rather than 46. The missing chromosome is an X chromosome. The affected person is always female.

Genetic profile

Turner syndrome is a disorder associated with characteristic defects in the X chromosome. The most common presentation is a female with a single X chromosome and an absent X chromosome. A Greek study from 1999 reported that the intact X chromosome was as likely to come from the mother as from the father. This means that there is no parental pattern of responsibility for the missing or defective X chromosome.

Another less common genetic pattern for Turner syndrome (35%) is a mosaic. A Danish study reported that mosaicism has an effect on malformations that are associated with Turner syndrome. Research reported in 1997 noted that the **karyotype** can have a significant effect on the growth of children with Turner syndrome.

The exact location of the genes on the X chromosome involved in Turner syndrome has not been determined as of 2001. At present, evidence exists that there is a locus for stature on the distal portion of the short arm; there are loci for normal ovarian function on both the short and long arms; and there are loci contributing to fetal viability on the long arm of X.

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Mosaic—A term referring to a genetic situation in which an individual's cells do not have the exact same composition of chromosomes. In Down syndrome, this may mean that some of the individual's cells have a normal 46 chromosomes, while other cells have an abnormal 47 chromosomes.

Ovary—The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

Zygote—The cell formed by the uniting of egg and sperm.

Demographics

The prevalence of Turner syndrome is widely reported as being approximately one per 2,000 live female births although researchers have reported prevalence rates that range from one in 3,125 to one in 5,000 live female births.

About 1-2% of all female conceptions have a missing X chromosome. Of these, the majority (99%) spontaneously abort, usually during the first trimester of pregnancy. With ultrasound being used more frequently, researchers have realized that some pregnancies with a missing X chromosome that progress into the second trimester are associated with nuchal cysts, severe lymphedema, or **hydrops fetalis**. These pregnancies are associated with a high frequency of fetal death.

Signs and symptoms

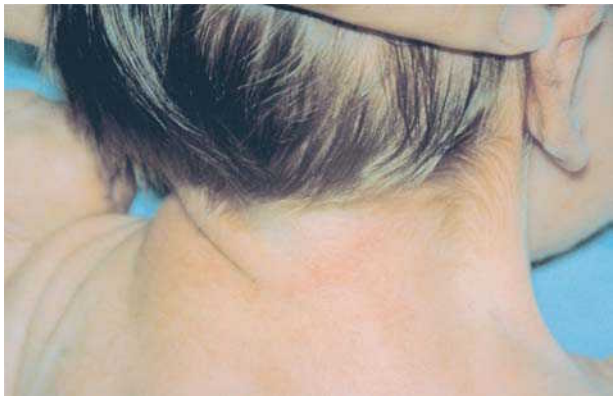
Turner syndrome is characterized by delayed growth that leads to a small stature and frequent infertility. Individuals with Turner syndrome report an increased incidence of fractures in childhood and osteoporotic fractures in adulthood. The incidence of **diabetes mellitus** (both insulin dependent and non-insulin dependent varieties) has been reported to be increased in Turner syndrome. Ischemic heart disease, stroke, and hypertension are also more common.

Growth in children with Turner syndrome is characterized by a slight intrauterine growth retardation, relatively normal growth rates for the first several years of life, a progressive deceleration of growth later in childhood, and the lack of a pubertal growth spurt. Growth patterns of Chinese girls with Turner syndrome parallel those of Caucasians, although their ultimate height is still less than normal.

Contrary to earlier reports, most individuals with Turner syndrome are not mentally retarded. They may have some learning disabilities, particularly with regard to spatial perception, visual-motor coordination, and mathematics. As a result, the nonverbal IQ in Turner syndrome tends to be lower than the verbal IQ.

Cardiovascular malformations are well-recognized congenital anomalies in Turner syndrome. Dilation and dissection of the aorta are reported in approximately half of women with Turner syndrome. Because of the potential consequences of aortic dilation, some experts recommend screening all individuals with Turner syndrome. However, the specific timing for this screening remains controversial in 2001.

Juvenile arthritis, an autoimmune condition, has been recently (1998) associated with Turner syndrome. The prevalence seems to be at least six times greater than would be expected if the two conditions were only randomly associated. Women with Turner syndrome have an



Females with Turner syndrome usually have a short neck with characteristic skin folds such as that shown here. *(Custom Medical Stock Photo, Inc.)*

elevated prevalence rate of dental caries and other periodontal conditions such as gum disease and plaque.

Normal pubertal development and spontaneous menstrual periods do not occur in the majority of children with Turner syndrome. It is estimated that 3-8% of girls with a single X chromosome and 12-21% of females with sex chromosome mosaicism may have normal pubertal development and spontaneous menstrual periods. A few pregnancies have been reported in women with Turner syndrome.

Diagnosis

Turner syndrome is diagnosed on the basis of genetic analysis of chromosomes. This can be done prior to birth. However, the predictive value of **amniocentesis** in diagnosing Turner syndrome varies from 21-67%. There is no significant relation between mother's age and risk of Turner syndrome.

Treatment and management

Because it is so dangerous, experts suggest screening for aortic dissection, although the specific timing for this screening is controversial. Plastic surgery to correct webbing of the neck should be considered at an early age (before entering school) for girls with Turner syndrome.

Most individuals with Turner syndrome require female hormone therapy to promote development of secondary sexual characteristics and menstruation. The time of beginning therapy varies with individuals. Experts recommend that therapy begin when a woman expresses concern about her onset of puberty.

All women receiving long term, exogenous female hormone therapy require periodic gynecological examinations because those with Turner syndrome have an increased risk of developing neoplasms such as gonadoblastoma and dysgerminoma, which arise from their rudimentary streak gonads.

Prognosis

Most women with Turner syndrome can live relatively normal lives. The prognosis for people with Turner syndrome is dependent on other conditions that may be present. Care must be taken to regularly monitor them for the health problems that are associated with Turner syndrome. For example, heart or kidney defects, hearing loss, or the development of inflammatory bowel disease may significantly impact the quality of life. Without these types of conditions, however, their life expectancy is normal. Support will be necessary to help an adolescent girl cope with body image issues and to help some women accept the fact that they will never be able to have children.

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ORGANIZATIONS

American Academy of Pediatrics. 141 Northwest Point Blvd., Elk Grove Village, IL 60007-1098. (847) 434-4000. Fax: (847) 434-8000. <http://www.aap.org/visit/contact.htm>.

Endocrine Society. 4350 East West Highway, Suite 500, Bethesda, MD 20814-4410. (301) 941-0200. Fax: (301) 941-0259. endostaff@endo-society.org.

Human Growth Foundation. 997 Glen Cove Ave., Glen Head, NY 11545. (800) 451-6434. Fax: (516) 671-4055. <http://www. hgf1@hgfound.org>.

MAGIC Foundation for Children's Growth. 1327 N. Harlem Ave., Oak Park, IL 60302. (708) 383-0808 or (800) 362-4423. Fax: (708) 383-0899. mary@magicfoundation.org. <http://www.magicfoundation.org/ghd.html>.

Turner Syndrome Society of Canada. 7777 Keele St, Floor 2, Concord, ONT L4K 1Y7. Canada (800) 465-6744 or (416) 660-7766. Fax: (416) 660-7450.

Turner Syndrome Society of England. 2 Mayfield Ave., London, W41PW. UK 44 (0)181-994 7625. Fax: 44 (0)181-995 9075. <http://www.exnet.com/staff/sys4/ts.html> or <http://www.tss.org.uk>.

Turner Syndrome Society of the United States. 14450 T. C. Jester, Suite 260, Houston, TX 77014. (800) 365-9944 or (832) 249-9988. Fax: (832) 249-9987. tesch@turner-syndrome-us.org. <http://www.turner-syndrome-us.org>.

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L. Fleming Fallon, Jr., MD, PhD, DrPH

Twin reversed arterial perfusion syndrome *see* **Acardia**

Twiner-Kieser syndrome *see* **Nail-Patella syndrome**

Type I diabetes *see* **Diabetes mellitus**

Type II diabetes *see* **Diabetes mellitus**

Typical arthrogryposis *see* **Distal arthrogryposis syndrome**

U

Urea cycle disorders

Definition

Urea cycle disorders are inborn errors in metabolism that can lead to brain damage and death. They involve a deficiency in one of the enzymes required by the urea cycle that removes ammonia from the blood.

Description

Ammonia accumulates in toxic levels if the urea cycle does not convert nitrogen from protein metabolism into urea for excretion into the urine. A series of biochemical reactions are necessary to complete the urea cycle. When an enzyme is missing or deficient, the cycle is interrupted and nitrogen accumulates in the form of ammonia. It cannot be excreted from the body and enters the blood stream, damaging nervous tissues, including the brain.

Seizures, poor muscle tone, respiratory distress, and coma follow if an affected infant is not treated. Acute neonatal symptoms are most frequently seen in boys with ornithine transcarbamylase, or OTC, deficiency. Mental retardation and even death may follow. People with partial deficiencies may not discover the problem until childhood or adulthood. Children may avoid meat or other protein foods. As ammonia levels rise in the body, individuals begin to show lethargy and delirium. Left untreated they may suffer a coma or death.

Sometimes young people with urea cycle disorders, who go undiagnosed, begin to show behavioral and eating problems. Those with partial enzyme deficiencies may experience episodes of high ammonia levels in the blood. This can occur after suffering from viral illnesses including chicken pox, or after eating high-protein meals, or even after significant physical exertion.

The incidence of adults with urea cycle disorders is increasing. Recent evidence has indicated that some people have survived undiagnosed into adulthood. They can suffer stroke-like symptoms, lethargy, and delirium. Without proper diagnosis and treatment, adults are at risk for permanent brain damage, coma, and death. Symptoms can appear after giving birth or after contracting a virus, and some adults have shown deficiencies after using the medication valproic acid (an anti-epileptic drug). Adult onset is more common in women with OTC deficiency.

Different enzymes may be lacking in the various forms of urea cycle disorders. The six major disorders of the urea cycle include:

- CPS–Carbamyl Phosphate Synthetase
- NAGS–N-Acetylglutamate Synthetase
- OTC–Ornithine Transcarbamylase
- ASD–Argininosuccinic Acid Synthetase (Citrullinemia)
- ALD–Argininosuccinase Acid Lyase (Argininosuccinic Aciduria)
- AG–Arginase

Genetic profile

All of these disorders are inherited as autosomal recessive traits except for ornithine transcarbamylase (OTC) deficiency. It is inherited as an X-linked trait, from the mother.

KEY TERMS

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Urea cycle—A series of complex biochemical reactions that remove nitrogen from the blood so ammonia does not accumulate.

Demographics

It is estimated the incidence of urea cycle disorders is about one in 30,000 births. Males and females are affected equally, except for the OTC deficiency which is more prevalent in males due to the fact that it is an X-linked disorder.

Signs and symptoms

In severe urea cycle disorders, rising ammonia levels cause irritability, vomiting, and lethargy within the first 24–72 hours of life. Seizures, poor muscle tone, respiratory distress, and coma follow if the infant is not treated. Acute neonatal symptoms are most frequently seen in boys with ornithine transcarbamylase, or OTC, deficiency. However, patients with mild or moderate urea cycle enzyme deficiencies may not show symptoms until early childhood.

Diagnosis

Early detection through blood testing is essential to prevent irreversible brain damage in severe cases of urea cycle disorders.

Treatment and management

Therapy consists of eating a diet that provides enough protein so the body gets the essential amino acids needed for growth, but not so much that toxic levels of ammonia are formed. Treatment may entail a protein restricted diet together with medications that provide alternative pathways for the removal of ammonia from the blood. These medications tend to be unpalatable and may be given by way of tube feedings. Blood tests are needed to monitor levels of ammonia, and hospitalizations may become necessary if levels rise to high.

Prognosis

With early detection and proper diet restrictions, individuals can lead relatively normal lives. However, irreversible brain damage can develop quickly in severe cases that go undetected.

Resources

ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

National Urea Cycle Disorders Foundation. 4841 Hill St., La Canada, CA 91001. (800) 38-NUCDF.

Julianne Remington

Usher syndrome

Definition

Usher syndrome is an inherited condition that causes hearing loss and a form of vision loss, called **retinitis pigmentosa** (RP), which worsens over time. Some people with Usher syndrome also have difficulties with balance and/or psychological problems. Although the symptoms of Usher syndrome were first described in 1858 by an ophthalmologist named Albrecht von Graefe, it was not until 1914 that it was well documented and recognized to be a genetic condition by another ophthalmologist, Charles Usher. There are three forms of Usher syndrome: type I, type II, and type III. Genetic research has shown there are many genes located on different **chromosomes**, all of which can lead to one of the types of Usher syndrome if they are altered.

Description

Usher syndrome is sometimes called hereditary deafness–retinitis pigmentosa, or retinitis pigmentosa and congenital deafness. Usher syndrome causes a specific type of hearing impairment called sensorineural hearing loss (SNHL). In order to understand how SNHL occurs, it is important to first understand how normal hearing works. The ear can be divided into three main parts: the outer ear, the middle ear, and the inner ear. The parts of the outer ear include the pinna (the visible portion of the ear), the ear canal, and eardrum. The pinna directs sound waves from the environment through the ear canal, toward the eardrum. The eardrum vibrates, and causes tiny bones (called ossicles), which are located in the middle ear, to move. This movement causes pressure changes in fluids surrounding the parts that make up the inner ear. The main structures of the inner ear are the cochlea and the vestibular system. These structures send information regarding hearing and balance to the brain. The cochlea is shaped like a snail shell, and it contains specialized sensory cells (called hair cells) that change the sound waves into electrical messages. These messages are then sent to the brain through a nerve (called the auditory nerve) that allows the brain to “hear” sounds from the environment. The vestibular system is a specialized organ that helps people maintain their balance. The vestibular system contains three structures called semicircular canals, which send electrical messages to the brain about movement and body position. This allows people to maintain their balance when moving by sensing changes in their direction and speed.

Sensorineural hearing loss occurs when parts of the inner ear (including the cochlea and/or auditory nerve) do not work correctly. The amount (or degree) of hearing

KEY TERMS

Central vision—The ability to see objects located directly in front of the eye. Central vision is necessary for reading and other activities that require people to focus on objects directly in front of them.

Cochlea—A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Peripheral vision—The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

Photoreceptors—Specialized cells lining the innermost layer of the eye that convert light into electrical messages so that the brain can perceive the environment. There are two types of photoreceptor cells: rod cells and cone cells. The rod cells allow for peripheral and night vision. Cone cells are responsible for perceiving color and for central vision.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

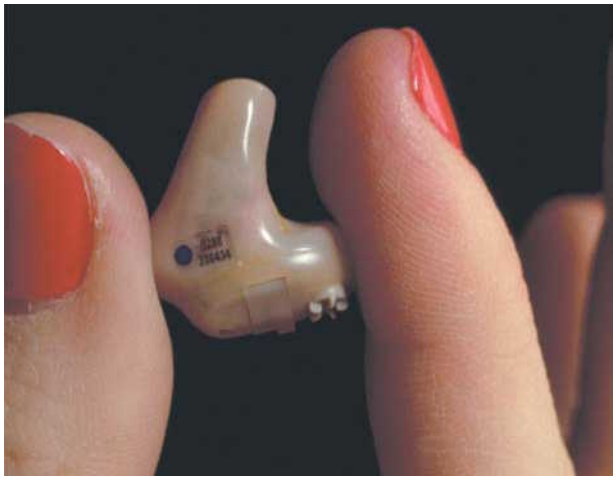
Sensorineural hearing loss (SNHL)—Hearing loss that occurs when parts of the inner ear, such as the cochlea and/or auditory nerve, do not work correctly. It is often defined as mild, moderate, severe, or profound, depending upon how much sound can be heard by the affected individual.

Vestibular system—A complex organ located inside the inner ear that sends messages to the brain about movement and body position. It allows people to maintain their balance when moving by sensing changes in their direction and speed.

loss can be described by measuring the hearing threshold (the sound level that a person can just barely hear) in decibels (dB). The greater a person's dB hearing level, the louder the sound must be to just barely be heard. Hearing loss is often defined as mild, moderate, severe, or profound. For people with mild hearing loss (26-45 dB), understanding conversations in a noisy environment, at a distance, or with a soft-spoken person is difficult. Moderate hearing loss (46-65 dB) causes people to have difficulty understanding conversations, even if the environment is quiet. People with severe hearing loss (66-85 dB) have difficulty hearing conversation unless the speaker is nearby or is talking loudly. Profound hearing loss (>85 dB) may prevent people from hearing sounds from their environment or even loud conversation. People with Usher syndrome generally have moderate, severe or profound SNHL, depending upon the type (I, II, or III) diagnosed.

Usher syndrome also causes a specific type of vision loss called retinitis pigmentosa (RP). In order to understand how RP occurs, it is helpful to first understand how normal vision works. The eye is made up of many different types of cells and tissues that all work together to send images from the environment to the brain, similar to the way a camera records images. When light enters the eye, it passes through the lens and lands on the retina, a very thin tissue lining the inside of the eye. The retina is actually made up of 10 different layers of specialized cells, which allow the retina to function similarly to film in a camera, by recording images. There is a small, yellow-pigmented area called the macula, located in the back of the eye in the center of the retina. The retina contains many specialized cells called photoreceptors, which sense light coming into the eye and convert it into electrical messages that are then sent to the brain through the optic nerve. This allows the brain to "see" the environment.

The retina contains two types of photoreceptor cells: rod cells and cone cells. Rod cells are located primarily outside of the macula and they allow for peripheral (side) and night vision. Most of the photoreceptor cells inside of the macula, however, are the cone cells, which are responsible for perceiving color and for viewing objects directly in front of the eye (central vision). If the retina is diseased, as in RP, night vision and peripheral vision are altered. This happens in RP because the rod and cone cells degenerate (breakdown) and die over time, resulting in night blindness and decreased peripheral vision (also called "tunnel vision"). People with Usher syndrome develop RP at different ages depending upon the type (I,



Hearing aids are medical devices that amplify sound for individuals experiencing hearing loss. *(Custom Medical Stock Photo, Inc.)*

II, or III) diagnosed. Although most people with Usher syndrome have fairly good vision before they reach their 30s, it worsens slowly over time and approximately 75% of people in their 70s are blind.

Usher syndrome type I

People with Usher syndrome type I are born with profound SNHL that occurs in both ears. As a result, they do not learn to speak, and typically learn to use sign language to communicate with others. Hearing aids usually are not very helpful, due to the amount of hearing loss present. However, some individuals benefit from a procedure called cochlear implantation, in which a small electronic device is surgically placed behind the ear (underneath the skin) and is attached to a wire that stimulates the inner ear, allowing people to hear useful sounds.

Usher syndrome type I also causes vestibular areflexia, which means affected individuals have balance problems because they cannot sense changes in direction or speed when they are moving. This causes children to develop certain skills that involve motion (such as walking) more slowly, to be clumsier, and to have a hard time with activities that require good balance (such as riding a bicycle). As affected people age, they tend to have an ataxic gait, which means they tend to stumble and shuffle their feet when walking.

The visual problems caused by RP usually develop during childhood among people with this type of Usher syndrome, and they gradually worsen over time. Usually the rod cells in the peripheral retina are affected first, causing night blindness and tunnel vision during childhood. Cone cells may eventually be affected, causing blind spots to develop. Eventually, vision loss worsens and affected people can have vision problems during the day. Cataracts (cloudiness in the lens of the eye) may also develop and cause decreased central vision. Although most people with this type of Usher syndrome do not become completely blind, worsening vision may make communication via sign language and lip reading difficult.

Mental retardation and psychiatric problems (such as **depression**, **bipolar disorder**, and psychosis) have been diagnosed in a number of people with Usher syndrome type I as well. Although some authors believe that the stress of losing both hearing and vision may lead to psychological problems, at least one study has suggested that these problems may be due to an overall smaller brain size that has been measured in some affected individuals.

Usher syndrome type II

People with Usher syndrome type II are born with mild to severe SNHL for low frequency sound that occurs in both ears. The SNHL is profound for higher frequency sounds. The amount of hearing loss is different between affected individuals, even those within the same family, although the ability to hear low frequency sound is often maintained. While hearing problems may worsen very slowly over time, speech therapy and the use of hearing aids are often helpful. Unlike people with type I, the vestibular (balance) system is not affected in people with Usher syndrome type II. Thus, they learn to walk on time as children (i.e. at approximately one year) and do not have problems with clumsiness. Although the symptoms of RP do occur among individuals with type II, they generally occur later in life (teenage years or later), compared to people with type I. Symptoms are similar, including night blindness, tunnel vision, blind spots, cataracts, and generally decreased vision. In addition, mental retardation, psychiatric problems, and decreased brain size have been seen in some people with Usher syndrome type II.

Usher syndrome type III

People with Usher syndrome type III may be born with normal hearing or mild hearing loss. However, their hearing loss is progressive, which means that it tends to worsen over time. The vestibular system causes mild balance problems that worsen over time among individuals with Usher syndrome type III. Older affected people may have balance problems similar to those seen in type I. There is a broad age range when the symptoms of RP occur among people with type III, although usually they happen later in life (late teens to early adult years). Vision problems also worsen over time. In addition, mental retardation and psychiatric problems also have been seen in some people with Usher syndrome type III.

People with Usher syndrome and their families often experience emotional and psychological distress. Depression, anger, and grief are common among affected teenagers and adults. The vision and hearing problems create ongoing challenges for people, in terms of their ability to receive information from the world and to effectively communicate with others. Affected people have to continually learn new skills, such as Braille or tactile sign language (i.e. using their hands to physically feel the signs), to adapt to their gradually worsening vision.

Genetic profile

Usher syndrome is inherited in an autosomal recessive manner. "Autosomal" means that males and females are equally likely to be affected. "Recessive" refers to a specific type of **inheritance** in which both copies of a person's **gene** pair (i.e. both alleles) need to have a change or "mutation" in order for the disease to develop. In this situation, an affected individual receives a mutated copy of the same gene from each parent. If the parents are not affected, they each have one working copy of the gene and one non-working (mutated) copy, and are only "carriers" for Usher syndrome. The chance that two carrier parents will have a child affected with Usher syndrome is 25% for each pregnancy. They also have a 50% chance to have an unaffected child who is simply a carrier, and a 25% chance to have an unaffected child who is not a carrier, with each pregnancy. In the United States, as many as one in every 70 people may be carriers of a mutation that can lead to Usher syndrome.

Although there are three recognizable types of Usher syndrome (I, II, and III), genetic research has shown that there are numerous genes, located on different chromosomes, that can all lead to Usher syndrome. This indicates that there is genetic heterogeneity among different families with Usher syndrome, meaning that different genes can lead to the same or similar disease among different families. As of February 2001, researchers have identified six different subtypes of Usher syndrome type I (USH1A, USH1B, USH1C, USH1D, USH1E, and USH1F), four subtypes of Usher syndrome type II (USH 2A, USH2B, USH2C, and USH2D), and one type of Usher syndrome type III (USH3). Although specific genes have been identified for only four of the 11 subtypes, the other seven have been linked to specific chromosomal regions.

Genetic Classification of Usher syndrome—February, 2001

- USH1A—Located on chromosome 14q32. Specific gene unknown.
- USH1B—Located on chromosome 11q13.5. Specific gene called myosin VIIA.
- USH1C—Located on chromosome 11p15.1. Specific gene called harmonin.
- USH1D—Located on chromosome 10q21-22. Specific gene called CDH23.
- USH1E—Located on chromosome 21q21. Specific gene unknown.
- USH1F—Located on chromosome 10. Specific gene unknown.
- USH2A—Located on chromosome 1q41. Specific gene called usherin.
- USH2B—Located on chromosome 3p23-24.2. Specific gene unknown.
- USH2C—Located on chromosome 5q14.3-21.3. Specific gene unknown.
- USH2D—Chromosome location unknown. Specific gene unknown.
- USH3—Located on chromosome 3q21-25. Specific gene unknown.

Although specific genes have been identified for some of the Usher syndrome subtypes (i.e. myosin VIIA, harmonin, CDH23, and usherin), not all mutations in these genes lead specifically to Usher syndrome. For example, although mutations in CDH23 can lead to Usher syndrome type 1D, some people who have certain types of mutations in both of their CDH23 gene copies have a form of autosomal recessive deafness (called DFNB12) in which affected individuals have profound SNHL at birth, but do not have balance or vision changes that are typically seen in Usher syndrome.

Demographics

It is estimated that 2.5 to 4.5 per 100,000 people are affected with Usher syndrome in various countries, including the United States, Denmark, Sweden, Norway, Finland, and Columbia, although it has been diagnosed in other parts of the world as well. There are some areas where Usher syndrome seems to be more common, including communities in northern Sweden and among the French Acadians in Louisiana. Certain types of Usher syndrome are more common in certain areas of the world as well. For example, among affected people in Finland, approximately 40% have type III. However, in the United States, types I and II are most common and occur with nearly equal frequency, while type III is very rare.

Signs and symptoms

Symptoms of Usher syndrome type I

- Profound hearing loss at birth, causing lack of speech
- Lack of vestibular function at birth, leading to delayed ability to walk and increased clumsiness

- Retinitis pigmentosa in childhood, causing night blindness, tunnel vision and decreased vision over time
- May cause mental retardation or psychiatric problems in some people

Symptoms of Usher syndrome type II

- Mild to severe hearing loss (for low-frequency sound) and profound hearing loss (for high-frequency sound) at birth
- Normal vestibular function, resulting in normal ability to maintain balance
- Retinitis pigmentosa in teens or early adult years, causing night blindness, tunnel vision and decreased vision over time
- May cause mental retardation or psychiatric problems in some people

Symptoms of Usher syndrome type III

- Normal hearing or mild hearing loss at birth that worsens over time
- Abnormal vestibular function, causing mild balance problems that worsen over time
- Retinitis pigmentosa by teenage or early adult years, causing night blindness, tunnel vision and decreased vision over time
- May cause mental retardation or psychiatric problems in some people

Diagnosis

As of February 2001, **genetic testing** is not readily available for people with Usher syndrome to look for their specific mutations (and thus confirm their diagnosis), in spite of the fact that a number of important genes have been identified. Some families do participate in genetic research studies by providing blood samples, with the hope that useful information may be learned about their genetic mutations, as well as Usher syndrome in general.

The diagnosis of Usher syndrome is based on the results from a variety of tests that measure hearing, vision, and balance. Sometimes the diagnosis is not made until a person with SNHL reaches adolescence and develops vision problems. A follow-up eye examination may allow an eye care specialist to detect changes seen in RP, thus confirming the diagnosis of Usher syndrome. Specialized testing of an affected person's vestibular system can be done to help determine the type of Usher syndrome as well.

Treatment and management

As of 2001, there is no cure for Usher syndrome. However, there are a number of ways to treat various symptoms.

Treatment and management of SNHL

Regular hearing exams are important to check for changes in hearing ability, especially for people with type II or type III Usher syndrome. Among people with milder forms of hearing loss, hearing aids and speech therapy are often useful. Sign language training for people with profound SNHL and their families provides a method of communication, although these skills need to be modified into tactile sign language as vision decreases. Some people with severe to profound forms of hearing loss may have cochlear implants placed in an effort to improve their perception of sound.

Treatment and management of RP

People with night blindness, tunnel vision and decreasing vision may benefit from a variety of techniques that help them cope with their ever-changing vision. The use of walking canes, guide dogs, magnifying lenses, flashlights, and Braille may be helpful. Specialized filtering lenses may decrease glare and make the eye more comfortable. Some people also find it useful to meet with low-vision specialists who can help them adapt to new lifestyle changes that help with daily living. Regular eye exams are important and allow early detection of cataracts, which may be treated with surgery.

Although there is no way to completely halt the symptoms of RP, studies published in the 1990s found that 15,000 IU of vitamin A palmitate can slow the course of the retinal changes among people with Usher syndrome type II. This therapy has not been recommended for people under 18 years of age, and women who may become pregnant need to discuss with their doctor the potential harms that vitamin A can cause for a developing baby. People who want to take the vitamin should speak with their doctor first and have regular blood tests to check vitamin levels as well as to rule out liver problems caused by the supplement.

There are a number of support groups available that provide education, support, and helpful advice to help people cope with the symptoms of Usher syndrome (see resources listed below).

Prognosis

Usher syndrome generally does not cause a shortened lifespan for affected individuals. Although people live for many years with Usher syndrome, the physical

symptoms and emotional side effects change over time. The vision problems usually worsen slowly over the years, forcing people to adapt their lifestyles, habits, and sometimes change professions. Regular eye exams can help diagnose cataracts that may be removed in an effort to maintain the best vision possible. Regular monitoring of hearing may be helpful for people with mild, moderate, and/or severe hearing loss, so that they can receive appropriate hearing aids. As vision problems (and sometimes hearing and/or balance problems) worsen, people are more likely to suffer emotionally, due to decreasing quality of life and independence. However, many low-vision devices, lifestyle modifications, and various support groups often provide much needed assistance to help maintain and/or improve quality of life for affected individuals.

Resources

BOOKS

Duncan, Earlene, et al. *Usher's Syndrome: What It Is, How to Cope, and How to Help.* New York: Charles C. Thomas Publisher, 1988.

Gorlin, R.J., H.V. Toriello, and M.M. Cohen. "Retinitis Pigmentosa and Sensorineural Hearing Loss (Usher Syndrome)." In *Hereditary Hearing Loss and Its Syndromes.* Oxford Monographs on Medical Genetics, No. 28. New York and Oxford: Oxford University Press, 1995.

Stiefel, Dorothy H., and Richard A. Lewis. *The Madness of Usher's: Coping With Vision and Hearing Loss/Usher Syndrome Type II.* Business of Living Publishing, 1991.

PERIODICALS

Keats, Bronya J.B., and David P. Corey. "The Usher Syndromes." *American Journal of Medical Genetics* 89, no. 3 (September 24, 1999): 158-166.

Kimberling, William J., Dana Orten, and Sandra Pieke-Dahl. "Genetic Heterogeneity of Usher Syndrome." *Advances in Oto-rhino-laryngology* 56 (December 2000): 11-18.

Miner, I.D. "People with Usher Syndrome, Type II: Issues and Adaptations." *Journal of Visual Impairment & Blindness* 91, no. 6 (November/December 1997): 579-590.

Miner, I.D. "Psychosocial Implications of Usher Syndrome, Type I, Throughout the Life Cycle." *Journal of Visual Impairment & Blindness* 89, no.3 (May/June 1995): 287-297.

Steel, Karen P. "New Interventions in Hearing Impairment." *British Medical Journal* 7235 (March 4, 2000): 622-626.

ORGANIZATIONS

American Council of the Blind. 1155 15th St. NW, Suite 720, Washington, DC 20005. (202) 467-5081 or (800) 424-8666. <http://www.acb.org>.

Boys Town National Research Hospital. 555 N. 30th St., Omaha, NE 68131. (402) 498-6749. <http://www.boystown.org/Btnrh/Index.htm>.

DB-LINK, Teaching Research. 345 N. Monmouth Ave., Monmouth, OR 97361. (800) 438-9376. <http://www.tr.wou.edu/dblink/about.htm>.

Foundation Fighting Blindness. Executive Plaza 1, Suite 800, 11350 McCormick Rd., Hunt Valley, MD 21031. (888) 394-3937. <http://www.blindness.org>.

Helen Keller National Center for Deaf-Blind Youths and Adults. 111 Middle Neck Rd., Sands Point, NY 11050. (516) 944-8900. <http://www.helenkeller.org/national/index.htm>.

Usher Family Support. 4918 42nd Ave. South, Minneapolis, MN 55417. (612) 724-6982.

Vestibular Disorders Association. PO Box 4467, Portland, OR 97208-4467. (800) 837-8428. <http://www.vestibular.org>.

WEBSITES

Sense homepage. <http://www.sense.org.uk/homepage.html>.

Pamela J. Nutting, MS, CGC

V

VACTERL *see* **VATER association**

Van der Woude syndrome

Definition

Van der Woude syndrome (VWS) is a condition affecting the lips, palate, and teeth. Depressions or pits typically are present on the lower lip at birth and cleft lip and/or cleft palate may also be present. Less commonly, certain teeth may not develop. VWS has previously been known as the lip pit syndrome.

Description

Van der Woude syndrome primarily involves pits developing on the lower lip, clefting of the lip and/or palate, and the absence of certain teeth. More than 80% or more than 8 out of 10 individuals with VWS will develop pits near the center of the lower lip and about 60–70% (6 to 7 people out of 10) will have a cleft lip and/or palate at birth. About half to two-thirds of the individuals will have both lower lip pits and a cleft of the lip and/or palate. In some cases, a cleft palate is present but is not immediately noticeable; this is called a submucosal cleft palate. The least common feature in VWS, missing teeth, is seen in about 10–20% (1 to 2 people out of 10) of individuals with VWS. The teeth most commonly affected are the second incisors and the second molars.

Van der Woude syndrome is related to another condition called popliteal pterygium syndrome (PPS). Popliteal pterygium syndrome is similar to VWS in that both conditions cause lip pits and cleft lip and/or palate to develop. Popliteal pterygium syndrome differs from VWS in that popliteal pterygium webs are present at birth. Pterygium means webbed skin. Popliteal refers to the back of the legs. Popliteal pterygium means that there is webbed skin on the back of the legs, usually on the back of the knees. Individuals with PPS may also have underdevelopment of the genitals, webbing between the fingers, adhesion of the lower and upper eyelids, and fibrous bands attaching the lower and upper jaws.

Some families have features consistent with both VWS and PPS. In other words, within a family, some family members have features that are entirely consistent with VWS and other family members have features consistent with PPS. Since the gene(s) causing VWS and PPS have not been identified, it is not known why these families have features of both diseases.

Genetic profile

Van der Woude syndrome follows autosomal dominant **inheritance**, indicating that every individual affected by VWS has a 50% (1 in 2) chance of passing on the condition to each of his or her children. Every individual inheriting the VWS **gene** will develop at least one feature of VWS. However, family members may develop different features, and some may develop very minor features whereas another family member may have more severe problems. In some cases, a family member's features may be so mild that he or she is initially thought to be unaffected. Apparently unaffected parents of a newborn with VWS should undergo a thorough examination since it is possible that one of the parents is very mildly affected. If such a parent is determined to be affected, all of his or her children will have a 50% chance of inheriting VWS.

As of 2001, the gene(s) involved in VWS have not been identified, although a specific region of chromosome 1 appears to be important in causing VWS. Research suggests that there may be at least one other gene, located on another chromosome, that may be important with regards to whether a cleft lip and/or palate develops. There is also evidence that VWS and PPS may be due to changes or mutations in the same gene or in neighboring genes on chromosome 1.

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Cleft—An elongated opening or slit in an organ.

Genetic test—Testing of chromosomes and genes from an individual or unborn baby for a genetic condition. Genetic testing can only be done if the gene is known.

Palate—The roof of the mouth.

Ultrasound examination—Visualizing the unborn baby while it is still inside the uterus.

Demographics

Van der Woude syndrome is a rare condition. Estimates of its incidence range from one in every 35,000 to one in every 200,000 live births. Males and females are affected equally.

Signs and symptoms

The primary symptom associated with VWS is the development of pits near the center of the lower lip (present in more than 80% of cases). In addition, 60–70% of individuals with VWS also have cleft lip and/or cleft palate. A few individuals (about 10–20%) with VWS are missing teeth, most commonly the second incisors and the second molars.

Diagnosis

As of 2001, diagnosis of VWS relies solely upon physical examination and whether or not the characteristic features of VWS are present or absent. The family history may also have an important role in determining the diagnosis. For example, if lower lip pits and a cleft palate are present in a newborn and no popliteal webs or other feature of PPS is present, then the child has VWS. If a newborn is born with a cleft palate only but has a family history of VWS, then the child most likely has inherited VWS.

As cleft lip and/or palate occurs in other genetic conditions as well as by itself, a newborn with this birth defect needs to be fully evaluated to ensure that the reason for the cleft is correctly determined. Likewise, lower lip pits may be seen in VWS, in PPS and rarely, in a third genetic condition called orofaciodigital syndrome, type 1; consequently, a baby born with lower lips pits needs to be fully evaluated.

Prenatal diagnosis for VWS can be attempted through ultrasound examination of unborn babies at risk for the condition. Cleft lip and very rarely cleft palate can be identified on ultrasound examination. However, as some clefts are small and some individuals with VWS do not have clefts at all, a normal ultrasound examination cannot completely rule out the chance the baby has inherited VWS. An ultrasound examination with high resolution, or a level 2 ultrasound, and an experienced technician may increase the chance of seeing cleft lips or palate. Lip pits cannot be seen on ultrasound examination, even with a higher resolution ultrasound. As of 2001, **genetic testing** of the unborn baby is not available as the gene(s) causing VWS have not been identified.

Treatment and management

An individual with VWS will be treated and followed according to the features he or she has developed. The lip pits seen in VWS rarely cause problems. Occasionally, saliva may ooze from the pits and if so, a fistula may have developed. A fistula is an abnormal passageway or opening that develops, and in VWS, a fistula may develop between a salivary gland located under the lip and the lip surface. The pits and fistulas may be surgically removed.

If a cleft lip and/or palate is present, surgery will be necessary to correct this problem. The treatment and management of cleft lips and palates in individuals with VWS is no different from cleft lips and palates occurring in other genetic conditions or by themselves. The child will need to be followed closely for ear and sinus infections and hearing problems. The child may need speech therapy and should be followed by a dentist and orthodontist. Counseling may be needed as the child grows up to address any concerns about speech and/or appearance.

Prognosis

Overall, individuals with VWS do well. If a cleft lip and/or palate is present at birth, there may be some feeding difficulties in the newborn period and in the following 3 to 6 months, until the cleft is corrected. However, once surgery repairing the cleft is completed, the child typically does well. Van der Woude syndrome is not associated with a shorter lifespan.

Resources

PERIODICALS

Nagore, Eduardo, et al. “Congenital Lower Lip Pits (Van der Woude Syndrome): Presentation of 10 Cases.” *Pediatric Dermatology* 15, no. 6 (November/December 1998): 443–445.

Rivkin, C.J., et al. "Dental Care for the Patient with a Cleft Lip and Palate. Part 1: From Birth to the Mixed Dentition Stage." *British Dental Journal* 188, no. 2 (January 22, 2000): 78–83.

ORGANIZATIONS

AboutFace USA. PO Box 458, Crystal Lake, IL 60014. (312) 337-0742 or (888) 486-1209. aboutface2000@aol.com. <http://www.aboutface2000.org>.

Family Village. Waisman Center, University of Wisconsin-Madison, 1500 Highland Ave., Madison, WI 53705-2280. familyvillage@waisman.wisc.edu. <http://www.familyvillage.wisc.edu/index.html>.

WideSmiles. PO Box 5153, Stockton, CA 95205-0153. (209) 942-2812. <http://www.widesmiles.org>.

Cindy L. Hunter, CGC

VATER association

Definition

VATER association describes a pattern of related birth defects in the same infant involving three or more of the following: vertebrae (spine), anus and rectum, heart, trachea (windpipe), esophagus, radius (bone of the arm), and kidneys. Infants can have any combination of features and there is a wide range of severity. Survival and medical complications depend on the extent and severity of features in each case.

Description

Quan and Smith first developed the term VATER association in 1973 to describe a similar pattern of birth defects in more than one infant. The problems at birth did not represent a certain syndrome but appeared to be associated since they were present in several babies. VATER is an acronym or abbreviation representing the first letter of each feature in the association: *V*ertebral (spine) abnormalities, *A*nal atresia (partial absence of the anus or unusual connection between anus and rectum), *T*racheo-*E*sophageal fistula (connection between the windpipe and the tube carrying food from mouth to stomach), and *R*adial (bone of the forearm) or *R*enal (kidney) differences.

In the 1970s some researchers expanded the VATER abbreviation to VACTERL. It was expanded to include *c*ardiac (heart) abnormalities, and *l*imb differences in general (differences in the arms and hands). In the expanded VACTERL, "L" includes radial differences and "R" represents kidney differences only. Both VATER and VACTERL are used to describe the same association of birth defects.

The exact cause of VATER is unknown. This is because VATER is rare and because the features vary from patient to patient. Many researchers agree that the cause of VATER occurs very early in the development of the embryo in order to affect so many organ systems. It is unknown whether VATER has a single cause or multiple causes during this early development process.

In the first couple of weeks after conception, a human embryo is a clump of cells that are unspecialized and full of potential. In the third week of pregnancy the embryo undergoes a process called gastrulation. This is when the cells of the embryo begin to group together in different areas. The different cell groups begin to specialize and prepare to form different organs and body parts. The mesoderm is the group of cells that organizes and eventually forms the baby's bones, muscles, heart, blood, kidneys, and reproductive organs. In the third week of pregnancy, the notochord also develops. The notochord is the future spinal cord and gives the early embryo a center and stability. It may also have a role in organizing other cell groups. The primitive gut also organizes in the fourth week. The primitive gut undergoes more specialization and division into zones called the foregut, midgut, and hindgut. The esophagus (tube from mouth to stomach) and trachea (windpipe) develop from the foregut. The anus and rectum develop from the hindgut. The constant cell movement, grouping, and specialization is a precise process. Any interruption or damage in this early stage can affect multiple organs and body structures.

Some researchers believe the cause of VATER is a problem with gastrulation. Other researchers believe the error occurs when mesoderm cells begin to move to areas to begin specialization. Another theory is that the mesoderm receives abnormal signals and becomes disorganized. Other researchers believe more than one error occurs in more than one area of the early embryo to produce VATER. Some also believe an abnormality of the notochord is involved in the development of VATER.

One group of researchers has discovered that pregnant rats that are given a toxic drug called adriamycin have offspring with birth defects very similar to those seen in humans with VATER. This has allowed the researchers to study normal and abnormal development of the early embryo. The study of rats showed abnormal notochord development in offspring with connections of the trachea and esophagus. In those offspring, the notochord was thickened and connected unusually to the foregut. More research of this animal model will answer many questions about the development and cause of the features of VATER.

KEY TERMS

Anus—The opening at the end of the intestine that carries waste out of the body

Fistula—An abnormal passage or communication between two different organs or surfaces.

Genetic profile

The exact genetic cause of VATER association is unknown. Most cases are sporadic and do not occur more than once in the same family. This was determined by studies of families with an affected individual. Since cases are rare and most are isolated in a family, studies to find a genetic cause have been unsuccessful. Parents of a child with VATER association have a 1% or less chance of having another baby with the same condition. There have been a few reports of affected individuals with a parent or sibling showing a single feature of the VATER spectrum. There has only been one reported case of a parent and child both affected with multiple VATER features.

Most individuals with VATER association have a normal chromosome pattern. However, a few cases of chromosome differences have been reported in individuals with VATER. One child with VATER had a deletion (missing piece) on the long arm of chromosome 6. Another male infant had a deletion on the long arm of chromosome 13. There have been other children reported with a chromosome 13 deletion and VATER-like features. This infant was the first reported with the deletion to have all of the VACTERL main features. He was also the first with this chromosome deletion to have a connection between his trachea and esophagus. Another child with VATER association had an extra marker chromosome. This is a fragment of chromosomal material present in the cell in addition to the usual 46 **chromosomes**. This child's marker was found to contain material from chromosome 12. These cases have not led to the discovery of a **gene** involved in VATER.

There has only been one VATER case reported in which a genetic change was identified. That female infant died one month after birth because of kidney failure. Her mother and sister later were diagnosed with a mitochondrial disease. Mitochrondria are the structures in the cell that create energy by chemical reactions. The mitochrondria have their own set of **DNA** and a person inherits mitochondrial DNA from the mother only. Stored kidney tissue from the deceased infant was analyzed and she was found to have the same genetic change in her mitochondrial DNA as her mother and sister. The researchers could not prove that the gene change caused the infant's features of VATER.

There are two subtypes of VACTERL that seem to be inherited. Both types have the typical VACTERL features in addition to hydrocephaly (excess water in the brain). They are abbreviated VACTERL-H. The first subtype was described in 1975 by David and O'Callaghan and is called the David-O'Callaghan subtype. It appears to be an autosomal recessive condition. Parents of an affected child are carriers of a normal gene and a gene that causes VACTERL-H. When both parents are carriers there is a 25% chance for an affected child with each pregnancy. The second subtype is called Hunter-MacMurray and appears to be an X-linked recessive condition. In X-linked conditions, the disease-causing gene is located on the X chromosome, one of the sex-determining chromosomes. Females have two X chromosomes and males have an X chromosome and a Y chromosome. A female who carries a disease-causing gene on one of her X chromosomes shows no symptoms. If a male inherits the gene he will show symptoms of the condition. A woman who carries the VACTERL-H X-linked gene has a 25% chance of having an affected son with each pregnancy. Both of these subtypes are rare and account for a small number of VACTERL cases.

Demographics

VATER is rare, but has been reported worldwide. Exact incidence can be difficult to determine because of different criteria for diagnosis. Some studies consider two or more VATER features enough to make the diagnosis. Other studies require at least three features to diagnose VATER. Also, infants with features of VATER may have other genetic syndromes such as trisomy 13, **trisomy 18**, **Holt-Oram syndrome**, **TAR syndrome**, and **Fanconi anemia**. VATER does appear to be more frequent in babies of diabetic mothers. It is also more frequent in babies of mothers taking certain medications during pregancy, including estroprogestins, methimazole, and doxorubicin.

Signs and symptoms

VATER has six defining symptoms. "V" represents vertebral abnormalities. Approximately 70% of individuals with VATER have some type of spine difference such as **scoliosis** (curvature of the spine), hemivertebrae (unusually aligned, extra, or crowded spinal bones), and sacral absence (absence of spinal bones in the pelvic area). Vertebral differences are usually in the lumbrosacral area (the part of the spine in the small of the back and pelvis). "A" represents anal atresia which is present in about 80% of individuals with VATER. This is an

unusual arrangment or connection of the anus and rectum. Imperforate anus is also common, in which the anal opening does not form or is covered. Babies with this problem cannot pass bowel movements out of the body. "TE" stands for tracheo-esophageal fistula. About 70% of babies with VATER have this problem. This is a connection between the two tubes of the throat—the esophagus (carries food from mouth to stomach) and the trachea (windpipe). This connection is dangerous because it causes breathing problems. These babies can also get food into their windpipe and choke. Lung infections are also common with this connection. Some infants may be missing part of their esophagus, causing problems with choking and feeding. These babies spit up their food because the food cannot get to the stomach.

In the original VATER association, "R" stood for radial differences and renal (kidney) problems. The radius is the forearm bone that connects to the hand on the side of the thumb. Radial differences can include an absent or underdeveloped radius. This often results in a twisted, unusual position of the arm and hand. The thumb can also be small, misplaced, or absent. Kidney problems are present in about half of individuals with VATER. These can include missing kidneys, kidney cysts, or fluid buildup in the kidneys. Some individuals also have an abnormal position of the urethra (the tube that carries urine out of the body).

The expanded VACTERL includes "C" for cardiac (heart) problems and "L" for limb differences. The heart problems are usually holes or other structural abnormalities. Limb differences usually involve the arms rather than the legs. The term includes more general differences such as extra fingers, shortened or missing fingers, and underdeveloped humerus (the bone of the upper arm). These differences often cause unusual arm or hand positions (bent or twisted) and fingers that are short, absent, or misplaced.

Many people have proposed an expanded VACTERL pattern to include differences of the reproductive system and absent sacrum. Small or ambiguous (not clearly male or female) genitalia, or misplaced reproductive parts are common in VACTERL. They tend to occur more frequently in infants with anal and kidney abnormalities. They are seen less often with esophagus and arm features. Absence of the bones of the sacrum (spine in the pelvis area) is also commonly seen in VACTERL.

Individuals with VATER have an average of seven to eight features or differences at birth. About two-thirds of features involve the lower body (intestines, genitals, urinary system, pelvis, and lower spine). One-third of features involve the upper body (arms, hands, heart, esophagus, and trachea). In addition to the typical VATER features, infants may have problems with the intestines or excess water in the brain. Intestinal problems (such as missing sections of intestine) are more common in individuals with anal or esophagus features.

Shortly after birth, infants with VATER often have failure to thrive. This involves feeding problems and difficulty gaining weight. Their development is often slow. Infants with visible signs of VATER should immediately be checked for internal signs. Quick detection of problems with the trachea, esophagus, heart, and kidneys can lead to earlier treatment and prevention of major illness. Most individuals with VATER have normal mental development and mental retardation is rare.

Diagnosis

Some features of VATER can be seen on prenatal ultrasound so that the diagnosis may be suspected at birth. Ultrasound can see differences of the vertebrae, heart, limbs, limb positions, kidneys, and some reproductive parts. Other problems that are associated with VATER on ultrasound are poor fetal growth, excessive fluid in the womb, absent or collapsed stomach, and one artery in the umbilical cord instead of the usual two. VATER features that cannot be seen on ultrasound are differences of the anus, esophagus, and trachea.

Even if VATER is suspected before birth, an infant must be examined after birth to determine the extent of features. The entire pattern of internal and external differences will determine if the infant has VATER association, another multiple birth defect syndrome, or a genetic syndrome (such as Holt-Oram syndrome, TAR syndrome, or Fanconi anemia). Since VATER overlaps with some genetic syndromes, some infants may fit the VATER pattern and still have another diagnosis. VATER only describes the pattern of related birth defects. Since the genetic causes of VATER are unknown, **genetic testing** is not available. A family history focusing on VATER features can help to determine if an infant has a sporadic case or a rare inherited case.

Treatment and management

Treatment for VATER involves surgery for each separate feature. Holes in the heart can be closed by surgery. Structural problems of the heart can also often be repaired. Prognosis is best for infants with small or simple heart problems. Some vertebral problems may also need surgery. If the vertebral differences cause a problem for the individual's posture, braces or other support devices may be needed.

Problems with the trachea and esophagus can also be repaired with surgery. Before surgery the infant

usually needs a feeding tube for eating. This will stop the choking and spitting up. The infant may also need oxygen to help with breathing. If the trachea and esophagus are connected, the connection is separated first. Once separated, the two trachea ends and esophagus ends can be sealed together. When part of the esophagus is missing, the two loose ends are connected. If the gap between the loose ends is too big, surgery may be delayed until the esophagus grows. Some infants still have problems after surgery. They may have a difficult time swallowing or food may get stuck in their throat. They may also have **asthma** and frequent respiratory infections.

Surgery can also repair problems of the anus and rectum. Before surgery, a temporary opening is made from the small intestine to the abdomen. This allows the infant to have bowel movements and pass stool material. An anal opening is created with surgery. The intestines and rectum are adjusted to fit with the new anal opening. The temporary opening on the abdomen may be closed immediately after surgery or it may be closed weeks or months later. Surgeons must be very careful not to damage the nerves and muscles around the anus. If they are damaged, the individual may lose control of their bowel movements.

Differences of the hands and arms can also be improved with surgery. Infants with underdeveloped or absent radius may have a stiff elbow, stiff wrist, or twisted arm. Surgery can loosen the elbow and wrist to allow for movement. The arm can also be straightened. If needed, muscles from other parts of the body can be put into the arm. This may also improve movement. Even after surgery, individuals may not have completely normal function of the muscles and tendons of the arms and hands.

Prognosis

Prognosis for individuals with VATER association depends on the severity of features. Infants with complex heart problems or severe abnormalities of the anus, trachea, or esophagus have a poorer prognosis. Infants with several features that require surgery have a higher death rate than infants that need minor surgery or no surgery. Survival also depends on how quickly internal problems are discovered. The sooner problems with the heart, anus, trachea, and esophagus are found and repaired, the better the outlook for the infant. One study estimated that infants with VATER have a death rate 25 times higher than healthy infants. Another study estimated that up to 30% of individuals with VATER die in the newborn period.

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ORGANIZATIONS

VACTRLS Association Family Network. 5585 CY Ave. Casper, WY 82604. <http://www.homestead.com/VAFN/VAFN.html>.

VATER Connection. 1722 Yucca Lane, Emporia, KS 66801. (316) 342-6954. <http://www.vaterconnection.org>.

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Amie Stanley, M.S.

Velocardiofacial syndrome *see* **Deletion 22q1 syndrome**

Ventriculomegaly *see* **Hydrocephalus**

Von Hippel-Lindau syndrome

Definition

Von Hippel-Lindau (VHL) syndrome is an inherited condition characterized by tumors that arise in multiple locations in the body. Some of these tumors cause **cancer** and some do not. Many of the tumors seen in VHL are vascular, meaning that they have a rich supply of blood vessels.

Description

In the mid-1800s, ophthalmologists described vascular tumors in the retina, the light-sensitive layer that lines the interior of the eye. These tumors, called *angiomas*,

KEY TERMS

Adrenal gland—A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

Angioma—A benign tumor composed of blood vessels or lymph vessels.

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Bilateral—Relating to or affecting both sides of the body or both of a pair of organs.

Broad ligament—The ligament connecting the ovaries to the uterus.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Epididymus—Coiled tubules that are the site of sperm storage and maturation for motility and fertility. The epididymis connects the testis to the vas deferens.

Hemangioblastoma—A tumor of the brain or spinal cord arising in the blood vessels of the meninges or brain.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Pancreatic islet cell—Cells located in the pancreas that serve to make certain types of hormones.

Pheochromocytoma—A small vascular tumor of the inner region of the adrenal gland. The tumor causes uncontrolled and irregular secretion of certain hormones.

Renal cell carcinoma—A cancerous tumor made from kidney cells.

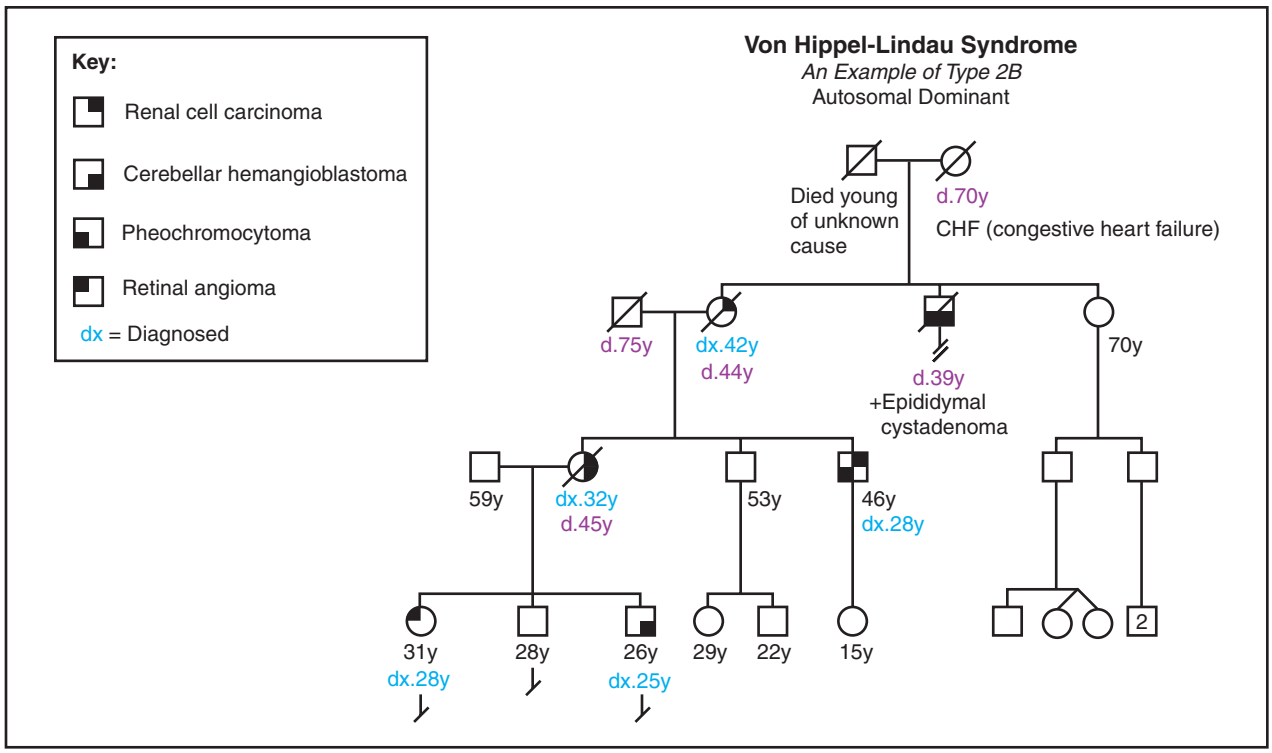
Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

were not cancerous but were associated with vision loss. In 1904, a German ophthalmologist named Eugen von Hippel noted that these retinal angiomas seemed to run in families. Twenty-three years later, Arvid Lindau, a Swedish pathologist, reported a connection between these retinal angiomas and similar tumors in the brain, called *hemangioblastomas*. Like angiomas, hemangioblastomas are vascular tumors as well. After Lindau noted this association, there were many more reports describing families in which there was an association of retinal angiomas and central nervous system (CNS) hemangioblastomas. Other findings were found to be common in these families as well. These findings included cysts and/or tumors in the kidney, pancreas, adrenal gland, and various other organs. In 1964, Melmon and Rosen wrote a review of the current knowledge of this condition and named the disorder von Hippel-Lindau disease. More recently, the tumors in the retina were determined to be identical to those in the CNS. They are now referred to as *hemangioblastomas*, rather than angiomas.

There are four distinct types of VHL, based on the manifestations of the disorder. Type 1 is characterized by all VHL-related tumors except those in the adrenal gland. Type 2 includes tumors of the adrenal gland and is subdivided into type 2A (without kidney tumors or cysts in the pancreas), type 2B (with kidney tumors and cysts in the pancreas), and type 2C (adrenal gland tumors only).

Genetic profile

VHL is inherited in an autosomal dominant manner. This means that an affected person has a 50% chance of passing the disease on to each of his or her children. Nearly everyone who carries the mutation in the VHL **gene** will show signs of the disorder, usually by the age of 65.



(Gale Group)

VHL is caused by a change or *mutation* in the VHL gene. This gene is located on chromosome 3 and produces the VHL protein. The VHL protein is a tumor suppressor, meaning that it controls cell growth. When the VHL gene is changed, the VHL protein does not function correctly and allows cells to grow out of control. This uncontrolled cell growth forms tumors and these tumors may lead to cancer.

People without VHL have two working copies of the VHL gene, one on each chromosome 3. Each of these copies produces the VHL protein. People affected with VHL inherit one working copy and one non-working copy of the gene. Thus, one gene does not make the VHL protein but the corresponding gene on the other chromosome continues to make the functional protein. In this case, cell growth will still be controlled because the VHL protein is available. However, as this person lives, another mutation may occur in the working gene. If this happens, the VHL protein can no longer be made. Cell growth cannot be controlled and tumors develop. Mutations like this occur in various organs at various times, leading to multiple tumors forming in distinct parts of the body over a period of time.

The majority of patients with VHL syndrome inherited the mutation from one of their parents. In approximately 1–3% of cases, there is no family history of the disorder and VHL occurs because of a new mutation in the affected individual. If a person appears to be an isolated case, it is important that the parents have **genetic testing**. It is possible that a parent could carry the mutation in the VHL gene but have tumors that do not cause any noticeable symptoms. If a parent is affected, each of his or her future children would have a 50% of being affected with VHL. If both parents test negative for the VHL **gene mutation**, each future child has a 5% risk of inheriting VHL. This small risk is to account for the rare possibility that one parent carries the mutation in his or her sex cells (egg or sperm) but does not express the disorder in any of the other cells of the body.

Demographics

VHL occurs in approximately one in 36,000 live births. It is seen in all ethnic groups and both sexes are affected equally.

Signs and symptoms

There are several characteristic features of VHL but no single, unique finding. Thus, it is necessary that many different specialties be involved in the diagnosis and

management of the disease. This approach will ensure proper, thorough care for these patients.

VHL is characterized by *hemangioblastomas*, tumors that arise in the blood vessel. These tumors are found in the central nervous system, or the brain and spinal cord. They most commonly present between the ages of 25 and 40 years and are the first symptom of VHL in 40% of cases. It is common to see multiple tumors. They may appear at the same time or at different times. These tumors generally grow slowly but, in some cases, may enlarge more rapidly. Hemangioblastomas seen in VHL are *benign* (non-cancerous) but may produce symptoms depending on their size, site, and number. Hemangioblastomas in the brain may lead to headache, vomiting, slurred speech, or unsteady and uncoordinated movements. These symptoms are usually due to the tumors disrupting brain function or causing increased pressure in the brain. Hemangioblastomas of the spine are usually accompanied by pain and can lead to loss of sensation and motor skills. Some of these tumors may fail to cause any observable symptoms.

In patients with VHL, hemangioblastomas also appear in the retina, the light-sensitive layer that lines the interior of the eye. These tumors occur in approximately half the cases of VHL and may be the first sign that a person is affected. It is common to see numerous retinal hemangioblastomas develop throughout a person's lifetime. They often can be found in both eyes. These tumors have been detected as early as the age of 4 years but are more typically found between the ages of 21 and 28 years. They often occur without symptoms, but can be detected on a routine eye exam. If untreated or undetected, they may cause the retina to detach from the eye. This condition is accompanied by bleeding and leads to vision loss and possibly blindness.

Approximately 50–70% of individuals with VHL also have numerous *cysts* on their kidneys. Cysts are sacs or closed cavities filled with liquid. In VHL, these cysts are vascular and frequently occur in both kidneys; however, they rarely result in noticeable symptoms. In some cases, these cysts may develop into *renal cell carcinomas*. These are cancerous tumors that are composed of kidney cells. Seventy percent of people affected with VHL will develop this type of kidney tumor during their lifetime. This type of cancer is generally diagnosed between the ages of 41 and 45 years. By the time this condition produces symptoms, it is likely that the cancer has already spread to other parts of the body. If this is the case, the tumors will respond poorly to chemotherapy and radiation, two common cancer treatments.

VHL can also cause multiple cysts in the pancreas. These occur at the average age of 41 years and are vascular in nature. Pancreatic cysts rarely cause problems and tend to grow fairly slowly. *Pancreatic islet cell tumors* can occur as well but are unrelated to the cysts. Islet cells in the pancreas produce *hormones*. Hormones are substances that are produced in one organ and then carried through the bloodstream to another organ where they perform a variety of functions. When tumors occur in the islet cells of the pancreas, these cells secrete too many hormones. This increase in hormones rarely leads to recognizable symptoms. Pancreatic islet cell tumors grow slowly and are non-cancerous.

Additionally, tumors in the adrenal gland, called *pheochromocytomas*, are common in VHL. The adrenal glands are located on top of each kidney. They secrete various hormones into the bloodstream. Pheochromocytomas are made of cells from the inner region of the adrenal gland. These tumors are benign but can be numerous and are often located in both adrenal glands. They can be confined to the inside of the adrenal gland or they can travel and appear outside of it. Some do not cause any observable symptoms. Others can lead to high blood pressure, sweating, and headaches.

In approximately 10% of cases, tumors can also be found in the inner ear. Most often, these tumors occur in both ears. They may lead to hearing loss of varying severity. This hearing loss may be one of the first signs that an individual is affected with VHL. Less commonly, a person may complain of dizziness or ringing in the ear due to these inner ear tumors.

Men with VHL commonly have tumors in the *epididymus*. The epididymus is a structure that lies on top of the testis and serves as the site for sperm storage and maturation for motility and fertility. If these tumors occur bilaterally, they can lead to infertility. However, as a general rule, they do not result in any health problems. The equivalent tumor in females is one that occurs in the broad ligament. This ligament connects the ovaries to the uterus. These tumors, however, are much less common than those in the epididymus.

It is important to note that wide variation exists among all individuals affected with VHL in regards to the age of onset of the symptoms, the organ systems involved, and the severity of disease.

Diagnosis

VHL can be diagnosed clinically, without genetic testing, in some cases. If a person has no family history of the disorder, a diagnosis of VHL can be made if one of the following criteria are met:

- the patient has two or more hemangioblastomas of the retina or CNS

- the patient has a single hemangioblastoma along with one of the other tumors or cysts that are commonly associated with the disorder

A diagnosis of VHL can also be established in a person who has a positive a family history of the disorder if they show one or more of the following before the age of 60:

- retinal hemangioblastoma
- CNS hemangioblastoma
- pheochromocytoma
- multiple pancreatic cysts
- tumor of the epididymus
- multiple renal cysts
- renal cell carcinoma

Several tests are available that can assist in the diagnosis of VHL. They can also determine the extent of symptoms if the diagnosis has already been made. A computed tomography (CT) scan or magnetic resonance imaging (MRI) are often utilized for these purposes. These procedures serve to produce images of various soft tissues in the body, such as the brain and abdominal area. In someone with VHL, they are used to assess for the presence of CNS hemangioblastomas and other tumors associated with the disorder, such as pheochromocytomas and inner ear tumors. Pheochromocytomas may also cause abnormal substances to be released into the urine. A urinalysis can detect these substances and, therefore, suggest the existence of these tumors. Additionally, ultrasound examination can assist in evaluating the epididymus, broad ligament, and kidneys. Ultrasound examination involves the use of high frequency sound waves. These sound waves are directed into the body and the echoes of reflected sound are used to form an electronic image of various internal structures.

VHL can also be diagnosed via examination of the VHL gene on the molecular level. This type of testing detects approximately 100% of people who are affected with the disorder and is indicated for confirmation of the diagnosis in cases of suspected or known VHL. Molecular genetic testing examines the VHL gene and detects any mutations, or changes, in the gene. Most often, in this disorder, the gene change involves a deletion of a part of the gene or a change in one of the bases that makes up the genetic code.

Since molecular testing is so accurate, it is recommended even in cases where the clinical criteria for diagnosis are not met. It is possible that the tumors associated with VHL are present but are not causing any observable symptoms. Thus, even if a person does not meet the diagnostic criteria mentioned above, molecular testing can be used as a means of "ruling out" VHL with a high degree of certainty. For patients with numerous, bilateral pheochromocytomas or for those who have a family history of these tumors, molecular testing is strongly suggested since these tumors may be the only signs of the disorder in those with VHL type 2C.

VHL can be diagnosed at various ages, ranging from infancy to the seventh decade of life or later. The age of diagnosis depends on the expression of the condition within the family and whether or not asymptomatic lesions are detected.

Treatment and management

There is no treatment for VHL because the genetic defect cannot be fixed. Management focuses on routine surveillance of at-risk and affected individuals for early detection and treatment of tumors.

For at-risk relatives of individuals diagnosed with VHL, molecular genetic testing is recommended as part of the standard management. If a person tests negative for the mutation, costly screening procedures can be avoided. If an at-risk relative has not been tested for the mutation, surveillance is essential for the early detection of signs of VHL.

The following groups of people should be routinely monitored by a physician familiar with VHL:

- individuals diagnosed with VHL
- individuals who are asymptomatic but who have tested positive for a mutation in the VHL gene
- individuals who are at-risk due to a family history of the disorder but have not undergone molecular testing

For these groups of people, annual physical examinations are recommended, along with neurologic evaluation for signs of brain or spinal cord tumors. Additionally, an eye exam should be completed annually, beginning around the age of five years. These exams can detect retinal hemangioblastomas, which often produce no clinical symptoms until serious damage occurs. When a person reaches the age of 16, an abdominal ultrasound should be completed annually as well. Any suspicious findings should be followed up with a CT scan or MRI. If pheochromocytomas are in the family history, blood pressure should be monitored annually. A urinalysis should be completed annually as well, beginning at the age of five. Although the majority of tumors associated with VHL are benign in nature, they all have a small possibility of becoming cancerous. For this reason, surveillance and early detection is very important to the health of those affected with VHL.

If any tumors are identified by the above surveillance, close monitoring is necessary and surgical intervention may be recommended. Hemangioblastomas of the brain

or spine may be removed before they cause symptoms. They may also be followed with yearly imaging studies and removed only after they begin to cause problems. Most of these tumors require surgical removal at some point and results are generally good. Retinal hemangioblastomas can be treated with various techniques that serve to decrease the size and number of these tumors.

Early surgery is recommended for renal cell carcinoma. Extreme cases may require removal of one or both kidneys, followed by a transplant. Additionally, pheochromocytomas should be surgically removed if they are causing symptoms. Inner ear tumors, however, generally are slow-growing. The benefit of removing one of these tumors must be carefully compared to the risk of deafness, which may result from the surgery. Epididymal and broad ligament tumors generally do not require surgery.

Prognosis

The average life expectancy of an individual with VHL is 49 years. Renal cell carcinoma is the leading cause of death for affected individuals. If an affected person is diagnosed with renal cell carcinoma, their average life expectancy decreases to 44.5 years. CNS hemangioblastomas are responsible for a significant proportion of deaths in affected individuals as well, due to the effects of the tumor on the brain.

Resources

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The VHL Handbook: What You Need to Know About VHL. Brookline, MA: VHL Family Alliance, 1999.

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ORGANIZATIONS

VHL Family Alliance. 171 Clinton Ave., Brookline, MA 02455-5815. (800) 767-4VHL. <http://www.vhl.org>.

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Mary E. Freivogel, MS

von Recklinghausen disease *see* **Neurofibromatosis**

von Willebrand disease

Definition

Von Willebrand disease is caused by a deficiency or an abnormality in a protein called von Willebrand factor and is characterized by prolonged bleeding.

Description

The Finnish physician Erik von Willebrand was the first to describe von Willebrand disease (VWD). In 1926 Dr. von Willebrand noticed that many male and female members of a large family from the Aland Islands had increased bruising (bleeding into the skin) and prolonged episodes of bleeding. The severity of the bleeding varied between family members and ranged from mild to severe and typically involved the mouth, nose, genital and urinary tracts, and occasionally the intestinal tract. Excessive bleeding during the menstrual period was also experienced by some of the women in this family. What differentiated this bleeding disorder from classical **hemophilia** was that it appeared not to be associated with muscle and joint bleeding and affected women and men rather than just men. Dr. von Willebrand named this disorder *hereditary pseudohemophilia*.

Pseudohemophilia, or von Willebrand disease (VWD) as it is now called, is caused when the body does not produce enough of a protein called von Willebrand factor (vWF) or produces abnormal vWF. vWF is involved in the process of blood clotting (coagulation). Blood clotting is necessary to heal an injury to a blood vessel. When a blood vessel is injured, vWF enables blood cells called platelets to bind to the injured area and form a temporary plug to seal the hole and stop the bleeding. vWF is secreted by platelets and by the cells that line the inner wall of the blood vessels (endothelial cells). The platelets release other chemicals, called factors, in response to a blood vessel injury, which are involved in forming a strong permanent clot. vWF binds to and stabilizes factor VIII, one of the factors involved in forming the permanent clot.

A deficiency or abnormality in vWF can interfere with the formation of the temporary platelet plug and also affect the normal survival of factor VIII, which can indirectly interfere with the production of the permanent clot. Individuals with VWD, therefore, have difficulty in forming blood clots and as a result they may bleed for longer periods of time. In most cases the bleeding is due to an obvious injury, although it can sometimes occur spontaneously.

VWD is classified into three basic types: type 1, 2, and 3 based on the amount and type of vWF that is pro-

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Biochemical testing—Measuring the amount or activity of a particular enzyme or protein in a sample of blood or urine or other tissue from the body.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Desmopressin (DDAVP)—A drug used in the treatment of von Willebrand's disease.

Diagnostic testing—Testing performed to determine if someone is affected with a particular disease.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

Endothelial cells—The cells lining the inner walls of the blood vessels.

Factor VIII—A protein involved in blood clotting that requires vWF for stability and long-term survival in the bloodstream.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Platelets—Small disc-shaped structures that circulate in the bloodstream and participate in blood clotting.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Skin hematoma—Blood from a broken blood vessel that has accumulated under the skin.

von Willebrand factor (vWF)—A protein found in the blood that is involved in the process of blood clotting.

duced. Type 1 is the most common and mildest form and results when the body produces slightly decreased amounts of typically normal vWF. Type 2 can be classified into five subtypes (A, B, M, N) and results when the body produces an abnormal type of vWF. Type 3 is the rarest and most severe form and results when the body does not produce any detectable vWF.

Genetic profile

The genetics of VWD are complex and involve a **gene** that produces vWF and is found on chromosome 12. Since two of each type of chromosome are inherited, children inherit two vWF genes. There are different types of changes in the vWF gene that can affect the production

of vWF. Some types of changes can cause the vWF gene to produce decreased amounts of normal vWF, while other changes can cause the gene to produce abnormal vWF. Most of the gene changes are significant enough that a change in only one vWF gene is sufficient to cause VWD. Some gene changes only cause VWD if both genes are changed, which often leads to more severe symptoms. Type 1 VWD is called an autosomal dominant condition since it is caused by a change in only one vWF gene. Since type 1 VWD results in only a slight decrease in the amount of vWF produced, the symptoms are often mild and even nonexistent in some patients. Most cases of Type 2 VWD are autosomal dominant since they are caused by a change in only one vWF gene that results in the production of an abnormal protein. An autosomal dominant form of VWD can be inherited from either parent or can occur spontaneously in the embryo that is formed when the egg and sperm cells come together during fertilization.

Some cases of type 2 VWD and all cases of type 3 VWD are autosomal recessive since they are caused by changes in both vWF genes. A person with an autosomal recessive form of VWD has inherited a changed gene from his or her mother and a changed gene from his or her father. Parents who have a child with an autosomal recessive form of VWD are called carriers, since they each possess one changed vWF gene and one unchanged vWF gene. Many carriers for the autosomal recessive forms of type 2 VWD and type 3 VWD do not have any symptoms, although some people with type 3 VWD are born to parents who have type 1 VWD and may have symptoms. Each child born to parents who are both carriers for VWD has a 25% chance of having VWD, a 50% chance of being a carrier, and a 25% chance of being neither a carrier nor affected with VWD disease. A person with an autosomal dominant form of VWD has a 50% chance of passing the changed gene on to his or her children who may or may not have symptoms.

Demographics

Approximately 1 out of 100 people are affected with VWD, making it the most common inherited bleeding disorder (hemophilia). VWD affects people of all ethnic backgrounds. Approximately 70–80% of people with VWD have type 1 and close to 20–30% have type 2. Type 3 is very rare and occurs in less than one percent of people with VWD.

Signs and symptoms

VWD is usually a relatively mild disorder characterized by easy bruising, recurrent nosebleeds, heavy menstrual periods, and extended bleeding after surgeries and invasive dental work. There is a great deal of variability in the severity of symptoms, which can range from clinically insignificant to life threatening. Even people within the same family who are affected with the same type of VWD may exhibit different symptoms. An individual with VWD may exhibit a range of symptoms over the course of his or her lifetime and may experience an improvement in symptoms with age. The severity of the disease is partially related to the amount and type of vWF that the body produces, but is also influenced by other genetic and nongenetic factors.

Type 1

Type 1, the mildest form of VWD, is usually associated with easy bruising, recurrent nosebleeds, heavy menstrual periods, and prolonged bleeding after surgeries and invasive work. Many people with type 1 VWD do not have any noticeable symptoms or only have prolonged bleeding after surgery or significant trauma. The amount of vWF produced by the body increases during pregnancy, so prolonged bleeding during delivery is uncommon in people with type 1 VWD.

Type 2

People with type 2 VWD usually have symptoms from early childhood and symptoms may even be present at birth. They usually experience prolonged bleeding from cuts, easy bruising, nose bleeds, skin hematomas, and prolonged bleeding from the gums following teeth extraction and minor trauma. More than 50% of women with type 2 VWD experience heavy periods that may require a blood transfusion. Gastrointestinal bleeding is rare but can be life-threatening. Some women with type 2 VWD exhibit prolonged bleeding during delivery.

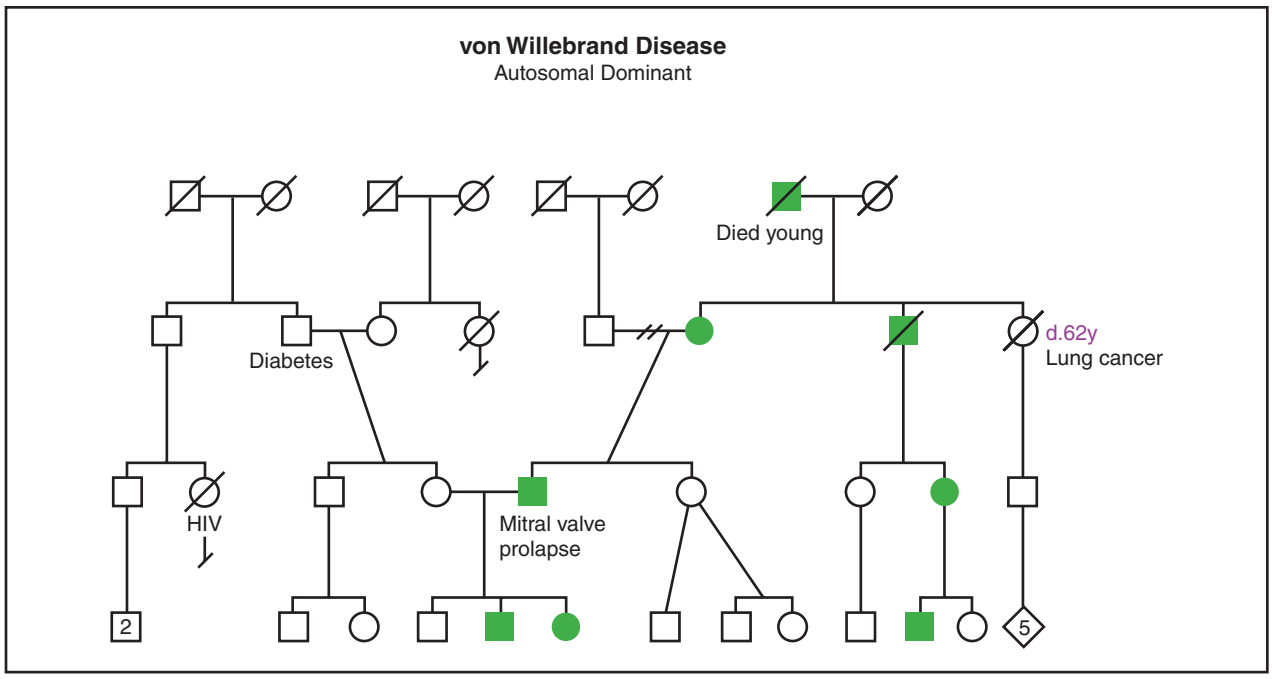
Type 3

Type 3 VWD can be quite severe and is associated with bruising and bleeding from the mouth, nose, intestinal, genital and urinary tracts. Type 3 is also associated with spontaneous bleeding into the muscles and joints, which can result in joint deformities. Some women with type 3 VWD experience prolonged bleeding during delivery.

Diagnosis

Diagnostic testing

Many people with VWD have mild symptoms or symptoms that can be confused with other bleeding disorders making it difficult to diagnose VWD on the basis of clinical symptoms. VWD should be suspected in any person with a normal number of platelets in their blood



(Gale Group)

and bleeding from the mucous membranes such as the nose, gums, and gastrointestinal tract. Testing for an individual with suspected VWD often includes the measurement of:

- how long it takes for the bleeding to stop after a tiny cut is made in the skin (the bleeding time)
- the amount of vWF (vWF antigen measurement)
- the activity of vWF (ristocetin co-factor activity)
- the amount of factor VIII (factor VIII antigen measurement)
- activity of factor VIII

People with type 1 VWD usually have an increased bleeding time but they may have an intermittently normal bleeding time. They also have a decreased amount of vWF, decreased vWF activity, and usually have slightly decreased factor VIII levels and activity. People with type 2 VWD have a prolonged bleeding time, decreased activity of vWF, and may have decreased amounts of vWF and factor VIII, and decreased factor VIII activity. Type 3 individuals have undetectable amounts of vWF, negligible vWF activity, factor VIII levels of less than 5–10%, and significantly reduced factor VIII activity. The activity of vWF is reduced for all types of VWD, making it the most sensitive means of identifying all three types of VWD. Patients with borderline results should be tested two to three times over a three month period.

Once a patient is diagnosed with VWD, further testing such as vWF multimer analysis and ristocetin-induced platelet aggregation (RIPA) may need to be performed to determine the subtype. Multimer analysis evaluates the structure of the vWF, and RIPA measures how much ristocetin is required to cause the clumping of platelets in a blood sample. The vWF multimer analysis is able to differentiate people with a structurally normal vWF (type 1) from people with a structurally abnormal vWF (type 2) and is often able to identify the subtype of patients with type 2 VWD. People with type 1 VWD usually have normal to decreased RIPA concentrations. Depending on the subtype, patients with type 2 VWD either have increased or decreased RIPA. RIPA is usually absent and the multimer analysis shows undetectable vWF in people with type 3 VWD.

In some cases DNA testing can be a valuable adjunct to biochemical testing. The detection of gene alteration(s) can confirm a diagnosis and can determine the type and subtype of VWD. It can also help to facilitate prenatal testing and testing of other family members. Unfortunately, as of 2001, many people with VWD possess DNA changes that are not detectable through DNA testing. A person who has a mother, father, or sibling diagnosed with VWD should undergo biochemical testing for VWD. If the relative with VWD possesses a detectable gene change, then DNA testing should also be considered.

Prenatal testing

If one parent has been diagnosed with an autosomal dominant form of VWD or both parents are carriers for an autosomal recessive form of VWD, then prenatal testing can be considered. If the parent with an autosomal dominant form of VWD possesses a detectable gene change or both parents who are carriers for an autosomal recessive form of VWD possess detectable mutations, then DNA testing of their fetus would be available. DNA testing can be performed through **amniocentesis** or chorionic villus sampling. If the DNA change in the parent(s) is unknown then prenatal testing can sometimes be performed through biochemical testing of blood obtained from the fetal umbilical cord, which is less accurate and is associated with a higher risk of pregnancy loss.

Treatment and management

VWD is most commonly treated by replacement of vWF through the administration of blood products that contain vWF or through treatment with desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin). DDAVP functions by increasing the amount of factor VIII and vWF in the bloodstream. Treatment with blood products or DDAVP may be started in response to uncontrollable bleeding or may be administered prior to procedures such as surgeries or dental work. The type of treatment chosen depends on the type of VWD and a patient's response to a preliminary treatment trial.

Treatment with desmopressin

DDAVP is the most common treatment for people with type 1 VWD. About 80% of people with type 1 VWD respond to DDAVP therapy. Treatment with DDAVP can also be used to treat some people with type 2 VWD. Patients with Type 2B VWD should not be treated with this medication since DDAVP can induce dangerous platelet clumping. Type 3 VWD should not be treated with DDAVP since this medication does not increase the level of vWF in type 3 patients. DDAVP should only be used in people who have been shown to be responsive through a pre-treatment trial transfusion with this medication.

DDAVP can be administered intravenously or through a nasal inhaler. DDAVP has relatively few side effects although some people may experience facial flushing, tingling sensations, and headaches after treatment with this medication. Often treatment with this medication is only required prior to invasive surgeries or dental procedures.

Treatment with blood products

Patients who are unable to tolerate or are unresponsive to drug-based treatments are treated with concentrated factor VIII obtained from blood products. Not all factor VIII concentrates can be used since some do not contain enough vWF. The concentrate is treated to kill most viruses, although caution should be used since not all types of viruses are destroyed. If the factor VIII concentrates are unable to manage a severe bleeding episode, then blood products called cryoprecipitates, which contain concentrated amounts of vWF, or platelet concentrates should be considered. Caution should be used when treating with these blood products since they are not treated to kill viruses.

Other treatments and precautions

Medications called fibrinolytic inhibitors can be helpful in the control of intestinal, mouth, and nose bleeding. Estrogens such as are found in oral contraceptives increase the synthesis of vWF and can sometimes be used in the long-term treatment of women with mild to moderate VWD. Estrogens are also sometimes used prior to surgery in women with type 1 VWD. Some topical agents are available to treat nose and mouth bleeds. Patients with VWD should avoid taking aspirin, which can increase their susceptibility to bleeding and people with severe forms of VWD should avoid activities that increase their risk of injury such as contact sports.

Prognosis

The prognosis for VWD disease is generally fairly good and most individuals have a normal lifespan. The prognosis can depend, however, on accurate diagnosis and appropriate medical treatment.

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Canadian Hemophilia Society. 625 President Kennedy, Suite 1210, Montreal, QUE H3A 1K2. Canada (514) 848-0503. Fax: (514) 848-9661. chs@hemophilia.ca. <http://www.hemophilia.ca/english/index.html>.

Haemophelia Society—Von Willebrand Support Services. Chesterfield House, 385 Euston Road, London, NW1 3AU. UK 0171 380 0600. Fax: 0171 387 8220. melissa@haemophilia-soc.demon.co.uk. <http://www.haemophilia-soc.demon.co.uk/vwd%20services1.html>.

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Vrolik type of osteogenesis imperfecta *see* **Osteogenesis imperfecta**

W

Waardenburg syndrome

Definition

Waardenburg syndrome (WS) encompasses several different hereditary disorders, the main features of which variably include abnormal pigmentation, hearing loss, and a subtle difference in facial features. Certain other physical anomalies occur less frequently in WS.

Description

In 1951, Dr. Petrus Waardenburg reported a syndrome of dystopia canthorum, heterochromia of the irides, and hearing loss. Dystopia canthorum (also called telecanthus) describes a subtle but unusual facial feature in which the inner corners of the eyes (canthi) are spaced farther apart than normal, yet the eyes (pupils) themselves are normally spaced. The result is that the eyes *appear* to be widely spaced, even though they are not. Heterochromia means *different-colored*, and irides is the plural form of iris—the colored portion of the eye. Thus, someone with heterochromia of the irides has different-colored eyes, often one brown and one blue. Another feature not originally noted by Dr. Waardenburg, but now considered a major sign of WS is a white forelock (white patch of hair extending back from the front of the scalp). In fact, disturbances in pigmentation (coloring) of various parts of the body are consistent features of WS. Uncommon but serious physical anomalies associated with WS include Hirschprung disease (intestinal malformation), **spina bifida**, cleft lip/palate, and musculoskeletal abnormalities of the arms.

Five types of WS have been defined based on clinical symptoms or genetic linkage. As of 2000, six different genes were associated with WS. Most families show autosomal dominant **inheritance**, but autosomal recessive inheritance and sporadic (single) cases are also seen. People with WS are not at increased risk for mental retardation, and vision loss is not more common. For the majority of those with WS, hearing loss is the only major medical problem they will have.

WS1 is the "classic" form of WS, and if someone uses just the name *Waardenburg syndrome* (with no modifying number), they are most likely referring to the

KEY TERMS

Dystopia canthorum—A wide spacing between the inner corners of the eyes, with the eyes themselves having normal spacing. Also called telecanthus.

Heterochromia irides—A medical term for individuals with different-colored eyes.

Hirschsprung disease—A deformation in which the colon becomes enlarged (megacolon), caused by abnormal nerve control of that portion of the large intestine.

Hypopigmentation—Decreased or absent color (pigment) in a tissue.

Neural crest cells—A group of cells in the early embryo, located on either side of the area that will eventually develop into the spinal cord. The cells migrate (move) away from the area and give rise to various body structures, including melanocytes (pigment producing cells), certain structures of the face and head, and parts of the nervous system.

Neurocristopathy—A disorder that results from abnormal development and/or migration of the neural crest cells in the embryo.

Sensorineural—Type of hearing loss due to a defect in the inner ear (sensing organ) and/or the acoustic nerve.

Synophrys—A feature in which the eyebrows join in the middle. Also called blepharophimosis.

group of disorders as a whole or just WS1. WS2 may occasionally be referred to as WS without dystopia canthorum. WS3 is also known as Klein-Waardenburg syndrome, as well as WS with upper limb anomalies. Alternate names for WS4 include Waardenburg-Hirschprung disease, Waardenburg-Shah syndrome, Shah-Waardenburg syndrome, and Hirschprung disease with pigmentary anomaly.

Genetic profile

Since Dr. Waardenburg's original description of his patients in 1951, many more families with the same or similar symptoms have been reported. By 1971, it became clear that a proportion of families have WS without dystopia canthorum. At that point, Waardenburg syndrome was divided into two distinct types, WS1 and WS2. In addition, a few individuals with typical signs of WS1 were found to also have musculoskeletal symptoms. This form of the disorder was named Klein-Waardenburg syndrome, now also known as WS3. Further, some researchers noted yet a different pattern of anomalies involving pigmentation defects and Hirschprung disease, which eventually became known as WS4. Finally, **genetic testing** of WS2 families has shown at least two subtypes—those that show genetic linkage are designated as WS2A and WS2B.

The four major types of WS have all been studied through **DNA** (genetic) analysis. There is some agreement between the clinical subtypes of WS and mutations in different genes, but genetic analysis has also served to confuse the naming scheme somewhat. The different types of WS, their inheritance patterns, and the genes associated with them, are listed below.

WS1

A number of different mutations in a single copy of the PAX3 **gene** on chromosome 2 are responsible for all cases of WS1, meaning it is always inherited as an autosomal dominant trait. The PAX3 gene plays a role in regulating other genes that have some function in producing melanocytes (pigment-producing cells). PAX3 was formerly known as the HUP2 gene.

WS2A

People who have typical signs of WS2 are designated as having WS2A only if genetic testing shows them to have a mutation in the MITF gene on chromosome 3. As with WS1, all cases of WS2A appear to be autosomal dominant. There is evidence that MITF is one of the genes regulated by PAX3.

WS2B

Some individuals with typical WS2 have had normal MITF gene analysis. A search for a different WS2 gene showed that some cases are linked to a gene on chromosome 1. This gene has been tentatively designated WS2B until its exact chromosomal location and protein product are identified. WS2B displays autosomal dominant inheritance.

WS3

Several people with a severe form of WS1 have been shown by genetic analysis to have a deletion of a small section of chromosome 2. Several genes are located in this section, including the PAX3 gene. Not all patients with WS3 have had the exact same genetic anomaly on chromosome 2, which may explain the variation in symptoms that have been reported. Some families with WS3 have displayed autosomal dominant inheritance, while other individuals with the condition have been sporadic cases.

WS4

Mutations in three different genes—EDNRB, EDN3, and SOX10 on **chromosomes** 13, 20, and 22 respectively—have been linked to WS4. Those cases of WS4 associated with the EDNRB and EDN3 show autosomal recessive inheritance, while the SOX10-associated cases are dominantly inherited.

Individuals with one of the autosomal dominant types of WS have a 50% risk of passing on the gene each time they have a child. A couple that has a child with WS4 linked to EDNRB or EDN3 faces a 25% risk for recurrence in each subsequent child. WS is quite variable, even within families. For instance, a parent with minimal pigment disturbance, mild facial features, and no hearing loss may have a child with pronounced physical features and deafness, and vice versa. There *may* be some correlation between specific gene mutations and the incidence of certain symptoms, but precise predictions are not possible.

As of 2000, the six genes listed above were those known to be associated with WS. It is expected, however, that more genes will be identified, especially since only a minority of WS2 cases have shown linkage to the MITF and WS2B genes.

Demographics

The prevalence of WS is estimated at one in 40,000. About 3% of all children with congenital deafness have WS. WS1 and WS2 occur with approximately the same frequency. WS3 and WS4 are much less common than

the other types. The majority of people with WS are Caucasian, but members of other ethnic groups may be affected as well.

Signs and symptoms

WS1

Dystopia canthorum is seen in 99% of people with WS1. Other facial features may include decreased length of the nasal bone, a broad/high nasal root (top of the nose), and increased length of the lower face. Seventy percent of people with WS1 have either a medial flare of the eyebrows or synophrys (joining of the eyebrows in the middle, also called blepharophimosis).

Some type of pigmentary disturbance is nearly always present, and involves hypopigmentation (decreased color) of the skin, hair, and/or irides. However, unlike the more common forms of **albinism** that often involve a generalized lack of pigment in the body, WS is characterized by patches of hypopigmentation—often termed "partial albinism." A white forelock or premature graying is seen in about 70% of people with WS1. The eyelashes and patches of body hair may also be hypopigmented. Heterochromia of the irides may be complete (25% of patients) or partial (5% of patients). In complete heterochromia, each eye is a different color. In partial heterochromia, an individual iris (in one or both eyes) is composed of two colors. Those people with WS1 who do not have iris heterochromia often have brilliant blue coloring of both eyes.

Although estimates vary, hearing loss of some type is present in about 60% of individuals with WS1. The true prevalence is difficult to determine because of the variable nature of the condition. About 80% of those with hearing loss are affected in both ears (bilateral). Profound hearing loss occurs in some 25% of all people diagnosed with WS1.

Spina bifida (open spine) is seen in a very small percentage of newborns with WS1, as is cleft lip/palate. Hirschprung disease, a deformation in which the colon becomes enlarged (megacolon), is a somewhat more frequent anomaly. Sprengel anomaly (elevated shoulder blade) can also be seen. Overall, about 10% of children with WS1 have one of these anomalies.

WS2

The major clinical distinction between WS1 and WS2 is the absence of dystopia canthorum in WS2. Otherwise, the conditions mostly differ by incidences of the various symptoms. The incidence of hearing loss in WS2 is 80%, with about 30% having a profound loss. Heterochromia of the irides occurs in 50% of patients. White forelock, premature graying, and hypopigmented skin patches are each found in about 15–20% of people with WS2. Synophrys occurs in only 5% of patients.

WS3

WS3 could be considered a subtype of WS1, since both are associated with the PAX3 gene. The distinction is clinical, with the added feature in WS3 being abnormalities of the muscles and bones of the arms. Some cases of WS3 have been sporadic. Several individuals diagnosed with WS3 have been in families where other members have typical signs of WS1. Thus, in some cases, WS3 can be considered a severe form of PAX3-associated WS, and is a dramatic example of the variability that can occur within families.

WS4

Individuals with WS4 usually do not have dystopia canthorum, and often do not have hearing loss. Hirschprung disease is the major distinguishing feature of WS4. In fact, individuals who carry a single abnormal EDNRB or EDN3 gene (as opposed to two abnormal copies of either gene in WS4) have only Hirschprung disease. A small proportion of people with WS4 have been found to have an abnormal SOX10 gene.

Diagnosis

In the early 1990s, a group of researchers known as the Waardenburg Consortium established criteria for diagnosing someone with WS1. They considered the major criteria of WS1 to be:

- congenital sensorineural hearing loss (not due to some other obvious cause)
- pigmentary disturbance of the iris
- hair hypopigmentation of some type
- dystopia canthorum
- an affected first-degree relative (parent, sibling, or child)

Minor criteria established by the Waardenburg consortium include:

- several areas of hypopigmented skin
- synophrys or medial flare of the eyebrows
- broad and high nasal root
- hypoplastic alae nasi (cartilage and skin around the nostrils)
- premature graying of hair

In order to be diagnosed with WS1, a person must have two major criteria, or one major plus two minor

TABLE 1

Waardenburg Syndrome

Type	Inheritance	Gene	Chromosome	Demographics	Symptoms
WS 1	AD	PAX3	2	1 in 40,000 for all types; WS 3 and WS 4 are less common than WS 1 and WS 2	Dystopia canthorum (99%) Medial flare of eyebrow or joining of eyebrows in the middle (70%) Hypopigmentation of skin, hair, and/or irides Heterochromia of irides (30%) Hearing loss (60%)
WS 2A	AD	MITF	3		Same symptoms as WS 1, but without dystopia conthorum Incidence of symptoms varies from WS 1, e.g. hearing loss (80%), heterochromia of irides (50%), joining of eyebrows (5%)
WS 2B	AD	"WS2B"	1		See WS 2A
WS 3	AD or sporadic	Deletions including PAX3	2		Similar symptoms to WS 1 but also features abnormalities of arm muscles and bones
WS 4	AR AR AD	EDNRB EDN3 SOX10	13 20 22		Usually dystopia canthorum is absent and incidence of hearing loss is reduced Hirschsprung disease

criteria. A modification of the list for WS2 includes removing dystopia canthorum, and including premature graying as a major criterion. With those modifications, a person with no family history of the condition should have two major criteria to be considered for WS2, and someone with an affected family member need only have one major criterion. Diagnosing WS2 can be more difficult than diagnosing WS1 because of the lack of dystopia canthorum. In addition, some people with a white forelock or premature graying may color their hair, and thus conceal an important sign.

As indicated, the distinction between WS1 and WS3 is clinical, with musculoskeletal anomalies added to the list of criteria for WS1. The criteria for diagnosing WS4 would be similar to those for WS2, with the inclusion of Hirschprung disease as a major criterion, and the *probable* exclusion of dystopia canthorum, broad nasal root, and severe hearing loss. In addition, by definition WS4 is not linked to PAX3, MITF, or WS2B, and is linked to one of the established WS4 genes (assuming genetic testing is available and informative).

Treatment and management

The primary medical consideration for people with WS is hearing loss. The most effective intervention is hearing aids. It is widely accepted that infants at risk for hearing loss, such as those who may inherit WS from a parent, can benefit from screening in the newborn period. An undiagnosed hearing deficit can result in delays in speech and learning. Children with profound hearing loss are eligible for special accommodations in their education, and the entire family can benefit by starting to use sign language very early.

Although spina bifida in WS is uncommon, the potential complications are serious. Infants with spina bifida usually have damage to the spinal cord at the level of the open spine, and consequently have either partial or total paralysis below that point. The opening in the spine can be repaired, but the neurological damage to the spinal cord is permanent. Cleft lip/palate is also uncommon in WS, but is a serious birth defect. Children with cleft lip/palate usually require several surgeries, but the outcome of the repair is generally very good. It would be prudent to screen any infant of a parent with WS for Hirschprung disease. Surgical removal or repair of the affected segment of colon is often necessary. Depending on the severity of the musculoskeletal anomalies, a child with WS3 might require some sort of orthopedic intervention, such as casting, bracing, or surgery. A few children with WS3 have had only minor joint contractures of the arms and hands.

Genetic counseling is indicated for any family with WS. Prenatal diagnosis might be an option if genetic testing in the family is informative, but many couples may

not choose invasive testing if they would not terminate a pregnancy for WS.

Prognosis

The majority of people with WS lead productive lives. In the absence of severe hearing loss, many people with WS would not be noticed as having a condition by anyone in the general population. If hearing loss is present, it usually does not get worse, and is often amenable to treatment. There is little hope for any preventive measures for WS, since all of the features of the syndrome occur early in embryonic development and are present at birth.

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Alexander Graham Bell Association for the Deaf, Inc. 3417 Volta Place NW, Washington, DC 20007-2778. (800) 432-7543. <http://www.agbell.org>.

FACES: The National Craniofacial Association. PO Box 11082, Chattanooga, TN 37401. (423) 266-1632 or (800) 332-2373. faces@faces-cranio.org. <http://www.faces-cranio.org/>.

National Association of the Deaf. 814 Thayer, Suite 250, Silver Spring, MD 20910-4500. (301) 587-1788. nadinfo@nad.org. <http://www.nad.org>.

National Organization for Albinism and Hypopigmentation. 1530 Locust St. #29, Philadelphia, PA 19102-4415. (215) 545-2322 or (800) 473-2310. <http://www.albinism.org>.

Research Registry for Hereditary Hearing Loss. 555 N. 30th St., Omaha, NE 68131. (800) 320-1171. <http://www.boystown.org/btnrh/deafgene.reg/waardsx.htm>.

Scott J. Polzin, MS

Walker-Warburg syndrome

Definition

Walker-Warburg syndrome is a congenital disorder of the central nervous system involving fatal neurological lesions. Multiple malformations of the brain, eyes, and muscle tissue distinguish WWS from similar malformation syndromes. It is also known by the acronym HARD +/- E syndrome (hydroencephalus, agyri, retinal **dysplasia**, plus or minus "e" for **encephalocele**).

Description

Affected individuals typically show a combination of severe brain, eye, and muscle defects. Multiple malformations of the brain include type II lissencephaly, a condition in which the brain lacks normal convolutions and is unusually smooth without folds. Eighty-four percent of the babies with WWS have macrocephaly (an enlarged head). In half of these cases, the macrocephaly is apparent at birth, and in a quarter of the cases it develops postnatally. **Hydrocephalus**, or excessive accumulation of cerebrospinal fluid around the brain, occurs in 95% of infants with WWS. This fluid fills abnormally large ventricles or spaces in the brain. Fifty percent of affected infants have an encephalocele, or gap in the skull that does not seal. The meninges or membranes that cover the brain may protrude through this gap. The formation of an encephalocele may be associated with the failure of the neural tube to close during development of the fetus. A malformed cerebellum characterizes the syndrome as well as distinct muscle abnormalities, including congenital **muscular dystrophy**.

Ocular defects occur in 100% of infants with WWS. The most common are abnormally small eyes and retinal abnormalities, which arise from the improper development of the light sensitive area at the back of the eye. Cataracts may also be present and more than three quarters of the infants born with WWS have a defect in the anterior chamber of the eye. WWS syndrome leads to severely retarded mental development and is often lethal in infancy.

Genetic profile

WWS is inherited in an autosomal recessive pattern. Offspring of parents who have had one affected infant have a 25% chance of having WWS. The locations of the causitive genes remains unknown.

Demographics

WWS is extremely rare. Cases described in the literature cite siblings with WWS born to consanguineous (closely related) parents as well as cases in families not known to be at risk.

Signs and symptoms

Clinical signs include a malformed head, small eyes, cataracts, retinal abnormalities, and muscle weakness. An

KEY TERMS

Agyri—A lack of convolutions or normal folds in the brain tissue.

Encephalocele—A gap in the skull through which membranes and brain tissue may protrude.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Retinal dysplasia—Improper development of the retina that can lead to detachment of the retina.

encephalocele may be present as well. Microscopic examination reveals that the cells and tissues of the brain develop in a highly disorganized fashion. Seizures may occur.

Diagnosis

Prenatal ultrasound can reveal some of the brain anomalies associated with WWS, most commonly hydrocephalus and encephalocele. Lissencephaly can not be diagnosed prenatally as normal fetal brains appear smooth. After birth, diagnosis is made on the basis of physical features and ultrasound exams. MRI may be used to confirm the smooth brain feature or type II lissencephaly typical of WWS. Genetic analysis helps distinguish WWS from Fukuyama-type congenital muscular dystrophy (FCMD), which has numerous similar features. WWS can be differentiated from other syndromes that display hydrocephalus or encephalocele by the presence of eye abnormalities including retinal defects, cataracts and anterior chamber defects. **Genetic testing** for Fukuyama-type congenital muscular dystrophy distinguished this from WWS.

Treatment and management

The severe malformations of the brain defy treatment and many infants with WWS die within the first year of life. Supportive care is required to provide comfort and nursing needs. Seizures may be controlled with medication. Shunting may be required to control the hydrocephalus. A shunt or short plastic tube can be placed to divert the excess cerebral spinal fluid to another area of the body where it can ultimately be absorbed by the body.

Genetic counseling is recommended for families at risk.

Prognosis

Patients have a very limited life expectancy and the syndrome is generally considered lethal. Most patients die before the age of two.

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Lissencephaly Network, Inc. 716 Autumn Ridge Lane, Fort Wayne, IN 46804-6402. (219) 432-4310. Fax: (219) 432-4310. lissennet@lissencephaly.org. <http://www.lissencephaly.org>.

National Hydrocephalus Foundation. 12413 Centralia, Lakewood, CA 90715-1623. (562) 402-3523 or (888) 260-1789. hydrobrat@earthlink.net. <http://www.nhfonline.org>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

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Julianne Remington

Ward-Romano syndrome *see* **Long-QT syndrome**

Weaver syndrome

Definition

Weaver syndrome is a congenital genetic syndrome associated with rapid growth beginning in the prenatal period as well as with a specific facial appearance and certain skeletal features. It has also been referred to as Weaver-Williams syndrome.

Description

Weaver syndrome was first described by Dr. David Weaver in 1974. A number of different symptoms occur in Weaver syndrome, however, it primarily results in rapid growth beginning in the prenatal period and continuing through the toddler years and into the elementary school years. It is also strongly associated with the bones developing and maturing more quickly (advanced bone age), a distinctive appearing face, and developmental delay. Babies often have a hoarse low-pitched cry.

Genetic profile

Weaver syndrome is for the most part a sporadic condition, meaning that a child affected by it did not inherit it from a parent. In a very few families, autosomal dominant **inheritance** has been reported, which means that both a parent and his/her child is affected by Weaver syndrome. The cause of Weaver syndrome is not known and the gene(s) that are involved in it have not been identified.

Demographics

Weaver syndrome is rare. About 30 to 50 cases have been published in the medical literature. It occurs in both males and females.

Signs and symptoms

Children with Weaver syndrome tend to have large heads. The faces of children with Weaver syndrome are usually very similar to each other, more so than to other family members, and include a round face, small chin, long philtrum (groove in the midline of the upper lip), large ears, and eyes that are father apart from each other than usual. Other common symptoms include hypertonia (increased muscle tone, tight muscles) as well as hypotonia (decreased muscle tone, "floppy" muscles) and a hoarse low-pitched cry in babies.

The excessive prenatal growth often results in the newborn being large with respect to weight, length and head circumference. The rapid growth continues through the toddler and youth years with the child's length and height often being above the 97th percentile, meaning that out of 100 children of the same age, the child is longer/taller than 97 of the children. There is very limited information on the rate of growth through adolescence and on final height, as most of the patients diagnosed with Weaver syndrome who have been reported in the medical literature have been children. In addition, given that the condition was first described 25 years ago, long-term clinical information is just becoming available.

There are a number of other features that have been associated with Weaver syndrome. The child may have difficulty extending elbows and knees completely, fingers and/or toes may be permanently flexed (camptodactyly) or have other problems such as overlapping fingers/toes or **clubfoot**, and the skin may appear loose. The child may have normal or delayed development; severe mental retardation is rarely seen. Speech may be delayed and when present, may be slurred. A child with Weaver syndrome may also have behavioral problems such as poor concentration, temper tantrums, which may be related to frustrations arising from communication problems, and obsessive and repetitive patterns of play.

Diagnosis

Diagnosis of Weaver syndrome is based solely upon clinical examination, medical history, and x ray data. There are no laboratory tests that can provide a diagnosis. The clinical criteria that are considered to be diagnostic for Weaver syndrome are excessive growth beginning in the prenatal and infancy period, a characteristic facial appearance, advanced bone age with the bones in the wrist being more advanced than other skeletal bones, metaphyseal flaring in the leg bones (the ends of the bone are wider than normal), and developmental delay.

There are many conditions and genetic syndromes that cause excessive growth, consequently, a baby and/or child who has accelerated growth needs to be thoroughly examined by a physician knowledgeable in overgrowth and genetic syndromes. The evaluation includes asking about health problems in the family as well as asking about the growth patterns of the parents and their final height. In some families, growth patterns are different and thus may account for the child's excessive growth. The child will also undergo a complete physical examination. The child will also be examined in terms of his/her facial appearance with special attention paid to the shape of his/her head, width of the face at the level of the eyes, and appearance of the chin and forehead. Besides measurement of the head circumference, arm

KEY TERMS

Advanced bone age—The bones, on x ray, appear to be those of an older individual.

Congenital—Refers to a disorder that is present at birth.

Developmental milestones—Infants and toddlers develop skills at certain ages. For example, by nine months, a child should be able to grasp and toss a bottle.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Metaphyseal flaring—A characteristic found only by x rays. If present, it means that the ends of the bone are wider than normal.

length, leg length, and wing span will also be measured. Laboratory testing may also be done. A chromosome analysis (**karyotype**) may be performed as well as testing for another genetic syndrome called fragile-X syndrome. The patient's bone age should also be assessed. Bone age is determined by x rays of the hand. It is known that a child's age can be predicted by the appearance of the wrist bones. In some cases the bones may develop or mature more quickly than normal, or in other words, the child's wrist bones appear to be those of an older child. This is referred to as advanced bone age. Advanced bone age is present in nearly every child with Weaver syndrome. It does not appear to result in other health problems. If the child begins to lose developmental milestones or appears to stop developing, metabolic testing may be done to evaluate for a metabolic condition called Sanfilippo syndrome. Developmental milestones refer to the skills infants and toddlers acquire as they get older, such as smiling, cooing, grasping toys, rolling over, walking, and talking.

Treatment and management

There is no cure for Weaver syndrome. However, the symptoms that cause problems can be treated and managed. Surgery may be used to correct any skeletal problems such as clubfoot or finger or toe problems. Physical and occupational therapy may help with muscle tone. Speech therapy may help with speech, and behavioral assessments and treatments may help with behavioral problems.

Prognosis

With appropriate treatment and management, children with Weaver syndrome appear to do well. Intellectually, most individuals with Weaver syndrome are normal. Weaver syndrome is not associated with a shortened life span.

Resources

BOOKS

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ORGANIZATIONS

Sotos Syndrome Support Group. Three Danda Square East #235, Wheaton, IL 60187. (888) 246-SSSA or (708) 682-8815 <http://www.well.com/user/sssa/>.

Weaver Syndrome Families Support (WSFS). 4357 153rd Ave. SE, Bellevue, WA 98006 (425) 747-5382.

WEBSITES

Genetic and Rare Conditions Site. <http://www.kumc.edu/gec/support/>.

Pediatric Database (PEDBASE). <http://www.icondata.com/health/pedbase/index.htm>.

The Family Village. <http://www.familyvillage.wisc.edu/index.htmlx>.

Cindy L. Hunter, CGC

Weaver-Williams syndrome *see* **Weaver syndrome**

Weissenbacher-Zweymuller syndrome

Definition

Weissenbacher-Zweymuller syndrome (WZS) is a genetic form of dwarfism in which affected individuals are born with small, underdeveloped jaws (micrognathia), cleft palate, short arms and legs (rhizomelia), "dumbbell" shaped arm and leg bones, protruding wide spaced eyes (hypertelorism), and incompletely formed back bones (vertebral coronal clefts). Unlike most other forms of dwarfism, individuals affected by Weissebacher-Zweymuller start out being affected by dwarfism, and then have a period of gradual growth and bone change that leads to normal physical development by age 5–6 years.

Description

Weissenbacher-Zweymuller syndrome refers to a rare disorder of small underdeveloped jaws (micrognathia), delayed bone growth, and unusual bone formation first described in 1964 by Weissenbacher and Zweymuller. The formation of bones is delayed because an important structural component of bone called cartilage does not form correctly. Since bone development is delayed, early milestones like walking and physical growth are delayed. Due to cleft palate, many individuals affected by WZS have speech and language delays. In most cases, physical, motor, mental, and academic development is normal by five or six years of age. Alternate names sometimes used for WZS include Pierre Robin syndrome with fetal chondrodysplasia and heterozygous otospondylomegaepiphyseal **dysplasia** (OSMED).

Genetic profile

Weissenbacher-Zweymuller syndrome appears to be caused by a single change or mutation in a **gene** called COL11A2 located on the short arm of chromosome 6. The mutation in COL11A2 leads to the incorrect formation of collagen. Since collagen is an important structural part of cartilage and bone, a mutation in COL11A2 leads to the signs and symptoms of WZS. The specific mutation that leads to WZS is inherited in an autosomal recessive pattern. An autosomal recessive condition is caused by the **inheritance** of two abnormal copies of a gene.

In the 1970s and 1980s there was some confusion among geneticists who were uncertain if WZS is a separate syndrome or part of another genetic syndrome. Although this confusion is not completely resolved, in 1993 an important study compared WZS to other related genetic syndromes and concluded that WZS is a separate genetic disorder that should not be "lumped" into the category of other genetic syndromes like **Stickler syndrome**. Since that time, a 1998 genetic study found that WZS and another syndrome called otospondylomegaepiphyseal dysplasia (OSMED) appear to be caused by different mutations in the same gene. This finding led the authors to suggest that the term OSMED be used to encompass a broad category that includes WZS as "heterozygous" OSMED while the other syndrome now called OSMED should be called "homozygous" OSMED. Because it has been found that WZS results from both heterozygous and homozygous mutations, researchers have suggested that this disorder follows both autosomal dominant and autosomal recessive inheritance patterns.

Demographics

WZS is a very rare disorder. The ethnic origin of individuals affected by WZS is varied and is not specific to any one country or ethnic population.

Signs and symptoms

Signs and symptoms of Weissenbacher-Zweymuller syndrome include: short arms and legs (rhizomelia), short stature at birth, an underdeveloped jaw (micrognathia), cleft palate, widely spaced eyes (hypertelorism), protruding eyes, a "snub" nose (depressed nasal bridge), dumbbell shaped long leg and arm bones (widening of the metaphyses of long bones), and incompletely formed back bones (coronal cleft of the lumbar vertebrae). The most unique sign of WZS is the gradual improvement of these changes.

Diagnosis

Diagnosis of Weissenbacher-Zweymuller syndrome is usually made from physical examination by a medical geneticist and x rays of the legs, arms, and back. Careful charts of growth and development over time also help with diagnosis. Most characteristic of WZS is the gradual improvement in bone size, growth, and shape.

Prenatal diagnosis of WZS is difficult, but can sometimes be made through a level II ultrasound examination of bone growth in the late second to third trimester of pregnancy. **Genetic testing** may be available through an **amniocentesis** procedure if the exact mutations running in the family are known. In 2001, genetic testing is done on a research basis in most cases.

One of the most important aspects in the diagnosis of WZS is ruling out other diagnoses. Conditions can be eliminated based on features that are not seen in WZS or are missing in other syndromes. For example, other conditions that look like WZS usually have progressively worsening symptoms instead of WZS's characteristic catch-up growth. Additionally, most conditions resembling WZS are inherited in an autosomal dominant pattern through the family. In an autosomal dominant condition, only one copy of the gene for a particular condition is necessary for a person to experience symptoms of the condition. If a parent has an autosomal dominant condition, there is a 50/50 chance for each child to have the same or similar condition.

Conditions to rule out in differential diagnosis include:

- Stickler syndrome, in which affected individuals have eye problems and do not have short arms and legs at birth.

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Micrognathia—A term used to describe small, underdeveloped lower jaw and chin.

Rhizomelia—A term used to describe the physical growth difference of short arms and legs.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

- Kniest dysplasia, in which affected individuals do not have a underdeveloped jaw, but they do have eye abnormalities.
- **Marshall syndrome**, in which affected individuals have hearing and eye abnormalities but do not have short limbs at birth.
- Isolated **Pierre-Robin sequence**, in which individuals have an underdeveloped jaw and cleft palate alone without short arms and legs.
- Diastrophic dwarfism, in which affected individuals often have club feet, joint contractures, hypermobile thumbs, and non-bulbous bones.
- Metatropic dwarfism, which is characterized by visible changes of the trunk and short limbs as the spine flattens and the bones become progressively deformed.
- Traditional oto-spondylo-megaepiphyseal dysplasia (OSMED), which includes individuals affected by deafness and abnormal growth and development of the spine and growth plates at the end of the long bones (**spondyloepiphyseal dysplasia**) with large growth plates at the end of the long bones (epiphyses).

In conclusion, it is important to do a thorough and long-term physical examination, a family history, and test for growth, hearing, and eyesight before making a diagnosis of WZS.

Treatment and management

The symptoms of WZS can be treated through follow-up and careful evaluation by a pediatric medical geneticist during the first years of life. Especially important to check are eyesight, hearing, and growth. Specific craniofacial clinics can help individuals affected by cleft palate with surgery, speech, and other related issues. Physical, occupational, speech, and language therapy may be suggested to help reduce "catch-up" time and developmental delays. As with any other disorder that includes developmental delays, specialists providing physical and language therapy can assist in the decision on whether special classes may help an individual child develop academically.

Prognosis

The chance for an individual affected by WZS to have normal physical, motor, mental, and school development by age six or seven is very good. To help in this development, early intervention with physical, occupational, speech, and language therapy and special classes may be helpful. A detailed case report in 1991 notes that the intelligence of children with WZS is generally within normal range, though they may have mild to moderate intellectual delay in the preschool period. The same report notes that physical growth should be normal by age five or six.

Resources

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ORGANIZATIONS

Pierre Robin Network. PO Box 3274, Quincy, IL 62305. (217) 224-7480. <http://www.pierrerobin.org/index.html>.

Stickler Involved People. 15 Angelina, Augusta, KS 67010. (316) 775-2993. <http://www.sticklers.org/sip>.

WEBSITES

Cleft Palate Foundation. <http://www.cleftline.org/>.

Family Village. <http://www.familyvillage.wisc.edu/index.html>.

LPA (Little People of America) Online. <http://www.lpaonline.org/>.

Robin, Nathaniel H., and Matthew L. Warman. "Stickler Syndrome." *GeneClinic* <http://www.geneclinics.org/profiles/stickler/index.html>.

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Dawn A. Jacob, MS

KEY TERMS

Atherosclerosis—Hardening of the arteries caused by cholesterol and fat deposits. Increases risk of heart disease, stroke, and other complications.

Progeria—Genetic abnormality that presents initially as premature aging and failure to thrive in children.

Systemic sclerosis—A rare disorder that causes thickening and scarring of multiple organ systems.

Werner syndrome

Definition

Werner syndrome is a very rare, inherited disease that resembles premature aging. Since the **gene** responsible was discovered in the mid-1990s, Werner syndrome has greatly interested researchers as a possible model for the study of human aging. It is also being extensively studied for insights it may eventually supply into a number of other diseases including **cancer**, **diabetes mellitus**, and atherosclerosis.

Description

This syndrome is named for the German physician C.W. Otto Werner (1879-1936). Werner was a medical student in 1903 when he first observed the syndrome in four siblings, all about 30 years of age. The following year, Werner wrote about these observations in his "Inaugural Dissertation."

The clinical signs and symptoms of Werner syndrome start to appear during the teen or early adult years, after which patients appear to age rapidly and have a greater-than-usual chance of developing cancer, cardiovascular disease, or diabetes mellitus. By the time the patient is 30–40 years old, he or she has the look of old age. The most common cause of death is heart attack.

While in many ways the signs and symptoms of Werner syndrome resemble those of premature aging (referred to in adults as **progeria**), there are also some significant differences. For instance, the tumors commonly seen in Werner syndrome patients are commonly derived from the cells of the mesoderm, a middle layer of the embryo that gives rise to a variety of tissues including cartilage, muscle, bone, kidneys, and connective tissue. In normal aging, tumors are more likely to be derived from the epithelial cells that cover the body's exterior and line most of its hollow structures. **Osteoporosis** and soft-tissue calcium deposits are found both in Werner syndrome and normal aging, but the distribution of these conditions within the body is different in patients with Werner syndrome. In addition, patients with Werner syndrome do not generally experience symptoms of **Alzheimer disease** or premature cognitive decline, as do their aging counterparts in the general population.

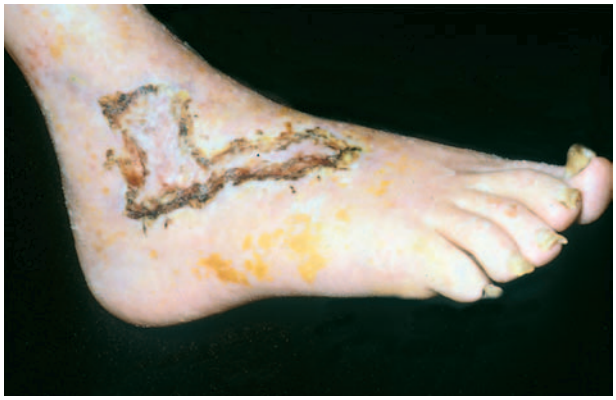
Researchers are uncertain whether the symptoms of Werner syndrome are really a speeding-up of normal aging, or whether the many similarities are coincidental. There is nonetheless considerable optimism that further research into Werner syndrome may lead to a better understanding of aging, cancer, diabetes, systemic sclerosis, atherosclerosis, cataracts, and other conditions.

Genetic profile

Werner syndrome results from mutation of a single gene. In 1992, the gene responsible (WRN) was mapped to chromosome 8p11-12. In 1996, a research group based in Seattle cloned the WRN gene. It was also discovered that the syndrome resulted from an autosomal recessive mutation that affects a member of a family of enzymes known as helicases that unwind deoxyribonucleic acid (**DNA**) and, in some cases, ribonucleic acid (**RNA**).

Despite the discovery that Werner syndrome is caused by a genetic defect, researchers are unable to explain exactly how this defect causes the disease. The purpose of helicases in the body is not fully understood, but they are known to unwind DNA, splitting the double-stranded molecules into separate single-stranded molecules. In this way, the enzymes are involved in the repair, recombination, replication, and transcription of DNA. There appear to be many damaged sites in DNA taken from patients with Werner syndrome. It has therefore been suggested that Werner syndrome may be caused by failure in these DNA-related processes, and that the somatic cells of those with Werner syndrome may be particularly prone to mutations.

The WRN gene is not known to bind to DNA damage, but recent research has suggested it might be able to sense the presence of damaged DNA. Since the discovery of the WRN gene, more than 10 mutations have been



Individuals with Werner syndrome often have skin abnormalities and may develop severe ulcerations, such as that seen on this foot. *(Custom Medical Stock Photo, Inc.)*

uncovered. Many of these mutations were in the Japanese population. It has been suggested that the relatively high incidence of Werner syndrome in that country may be related to traditions of marriages between closely related individuals in some areas of Japan.

As of 2001, researchers were seeking an animal model to allow them to further study Werner syndrome. Specifically, they hoped to create mice with a genetic equivalent of the WRN gene, and to determine whether these mice would age more quickly than normal mice.

Demographics

Because of the limited number of cases, the demographic distribution of Werner syndrome is difficult to determine. Estimates of the number of people affected range from one in 95,000 to one in 1,000,000 people. Unlike progeria, which can be diagnosed at birth or soon after, Werner syndrome is not usually detected prior to adolescence. It is commonly noticed only after patients have failed to undergo the normal growth spurt associated with their teen years. The full range of symptoms is not usually seen until patients reach their 20s or 30s. Werner syndrome is more common in families in which a close biological relationship exists between parents. It occurs equally in both sexes. There is no evidence of a birth-order effect.

Signs and symptoms

The cardinal signs and symptoms of Werner syndrome start to appear after the age of 10. They are:

- Cataracts. These occur in both eyes, and usually develop by age 25 or 30.
- Skin problems including tight, shiny, smooth skin, ulceration, general wasting of the skin and localized wasting of the subcutaneous area underneath it, pigmentary changes, a thickening of the horny outer layer of the skin, and a characteristic bird-like facial appearance, including a beaked or pinched nose and unusually prominent eyes.
- Shortness of stature.
- An affected sibling or a close biological relationship between parents (3rd cousin or closer).
- Earlier-than-usual graying and/or thinning of scalp hair, usually by age 20.
- Excess amounts of hyaluronic acid (more commonly found in the body's connective tissues and in the fluids of the eyes and joints) in the urine.

Additional signs and symptoms of Werner syndrome include the following:

- Diabetes mellitus. This is usually mild, but can be found in between 44% and 67% of Werner syndrome patients.
- Impaired function of the ovaries or testes, as indicated by small or poorly developed genitalia or reduced fertility.
- Osteoporosis, most commonly in the upper limbs and spine, as well as in the lower limbs, feet, and ankles. In patients with Werner syndrome, osteoporosis is unlikely to be found in the skull or the torso.
- Unusually high bone density in the extremities of the finger and toe bones. This must be established by an x-ray examination.
- Deposits of calcium salts in soft tissues of the body. Common locations are around the Achilles tendon and the tendons of the elbow and the knee.
- Evidence pointing to earlier-than-usual arterial disease, such as a prior heart attack or abnormal electrocardiograms, etc.
- Rare or multiple tumors, or tumors derived from the mesoderm, the middle layer of the embryo. Werner syndrome is not marked by increased occurrence of all forms of tumors, but by selectively higher proportions of certain cancers that are relatively rare.
- Changes to the voice, rendering it squeaky, hoarse, or high-pitched.
- Flat feet.

In addition to the above signs and symptoms used for formal diagnostic purposes, other clinical observations have been reported, including loss of eyelashes and eyebrow hair, nail deformities, as well as the presence of thin limbs with a stocky trunk. A possible link to lung cancer has also been proposed.

In some cases, Werner syndrome can occur in a slower and milder partial form, with only some of the symptoms present.

Diagnosis

A definite diagnosis of Werner syndrome is established by the presence of all of the cardinal signs and symptoms listed above, plus at least two of the additional signs and symptoms.

A probable diagnosis is indicated by the presence of all of the first three cardinal signs, plus any two from the additional list.

A possible diagnosis is suggested by the presence of either cataracts or the skin manifestations, plus any four of the other signs or symptoms.

Werner syndrome may be ruled out if the above signs and symptoms appear prior to adolescence. The exception to this rule is shortness of stature, because patterns of pre-adolescent growth are not sufficiently understood.

Diagnosis may involve x rays to study hormone excretion, skin biopsies, and a blood-sugar test to determine whether diabetes mellitus is present. Werner syndrome can also be diagnosed by mutational analysis of the WRN gene.

Treatment and management

There is no known cure for Werner syndrome, so treatment is related to the specific symptoms present. For example, cataracts can be corrected by surgery and skin ulcers can be treated with grafts.

Prognosis

Because it mimics the human aging process, Werner syndrome significantly reduces life expectancy in most patients. Average life expectancy for a Werner symptom patient is somewhere between 40 and 47 years. The most common causes of death are heart attacks, cerebrovascular accidents, and cancers.

Resources

BOOKS

Thoene, Jess G., ed. *Physicians' Guide to Rare Diseases.* 2nd ed. Montvale, NJ: Dowden Publishing Company Inc., 1995.

ORGANIZATIONS

International Progeria Registry. IBR Dept. of Human Genetics, 1050 Forest Hill Rd., Staten Island, NY 10314. (718) 494-5333. wtbibr@aol.com.

International Registry of Werner Syndrome. University of Washington Dept. of Pathology, Health Science Bldg K543, Box 357470, Seattle, WA 98195. (206) 543-5088. <http://www.pathology.washington.edu/werner/registry/frame2.html>.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. resourcecenter@modimes.org. <http://www.modimes.org>.

David L. Helwig

Whistling face syndrome *see* **Freeman-Sheldon syndrome**

Williams syndrome

Definition

Williams syndrome is a genetic disorder caused by a deletion of a series of genes on chromosome 7q11. Individuals with Williams syndrome have distinctive facial features, mild mental retardation, heart and blood vessel problems, short stature, unique personality traits, and distinct learning abilities and deficits.

Description

Williams syndrome, also known as Williams Beuren syndrome, was first described in 1961 by Dr. J.C.P. Williams of New Zealand. At that time it was noted that individuals with Williams syndrome had an unusual constellation of physical and mental findings. The physical features include a characteristic facial appearance, heart and cardiovascular problems, high blood calcium levels, low birth weight, short stature, and other connective tissue abnormalities. The intellectual problems associated with Williams include a mild mental retardation and a specific cognitive profile. That is, individuals with Williams syndrome often have the same pattern of learning abilities and disabilities, as well as many similar personality traits.

The findings in Williams syndrome are variable—that is, not all individuals with Williams syndrome will have all of the described findings. In addition to being variable, the physical and mental findings associated with Williams syndrome are progressive—they change over time.

Genetic profile

Williams syndrome is a genetic disorder due to a deletion of chromosome material on the long arm of

KEY TERMS

***de novo* deletion**—A deletion that occurs for the first time in the affected individual. The cause of de novo deletions is not known.

Hypercalcemia—High levels of calcium in the blood.

Stellate—A star-like, lacy white pattern in the iris. Most often seen in light-eyed individuals.

chromosome 7. A series of genes are located in this region. Individuals with Williams syndrome may have some or all of these genes deleted. Because of this, Williams syndrome is referred to as a contiguous **gene** deletion syndrome. Contiguous refers to the fact that these genes are arranged next to each other. The size of the deletion can be large or small, which may explain why some individuals with Williams syndrome are more severely affected than others. If you think of these genes as the letters of the alphabet, some individuals with Williams syndrome are missing A to M, some are missing G to Q and others are missing A to R. While there are differences in the amount of genetic material that can be deleted, there is a region of overlap. Everyone in the above example was missing G to M. It is thought that the missing genes in this region are important causes of the physical and mental findings of Williams syndrome.

Two genes in particular, ELN and LIMK1, have been shown to be important in causing some of the characteristic symptoms of Williams syndrome. The ELN gene codes for a protein called elastin. The job of elastin in the human body is to provide elasticity to the connective tissues such as those in the arteries, joints, and tendons. The exact role of the LIMK1 gene is not known. The gene codes for a substance known as lim kinase 1 that is active in the brain. It is thought that the deletion of the LIMK1 gene may be responsible for the visuospatial learning difficulties of individuals with Williams syndrome. Many other genes are known to be in the deleted region of chromosome 7q11 responsible for Williams syndrome and much work is being done to determine the role of these genes in Williams syndrome.

Williams syndrome is an autosomal dominant disorder. Genes always come in pairs and in an autosomal dominant disorder, only one gene need be missing or altered for an individual to have the disorder. Although Williams syndrome is an autosomal disorder, most individuals with Williams syndrome are the only people in their family with this disorder. When this is the case, the chromosome deletion that causes Williams syndrome is called *de novo*. A *de novo* deletion is one that occurs for the first time in the affected individual. The cause of *de novo* chromosome deletions is unknown. Parents of an individual with Williams syndrome due to a *de novo* deletion are very unlikely to have a second child with William syndrome. However, once an individual has a chromosome deletion, there is a 50% chance that he or she will pass it on to their offspring. Thus individuals with Williams syndrome have a 50% chance of passing this deletion (and Williams syndrome) to their children.

Demographics

Williams syndrome occurs in 1 in 20,000 births. Because Williams syndrome is an autosomal dominant disorder, it affects an equal number of males and females. It is thought that Williams syndrome occurs in people of all ethnic backgrounds equally.

Signs and symptoms

Williams syndrome is a multi-system disorder. In addition to distinct facial features, individuals with Williams syndrome can have cardiovascular, growth, joint, and other physical problems. They also share unique personality traits and have intellectual differences.

Infants with Williams syndrome are often born small for their family and 70% are diagnosed with failure to thrive during infancy. These growth problems continue throughout the life of a person with Williams syndrome and most individuals with Williams syndrome have short stature (height below the third percentile). Infants with William syndrome can also be extremely irritable and have "colic-like" behavior. This behavior is thought to be due to excess calcium in the blood (hypercalcemia). Other problems that can occur in the first years include strabismus (crossed eyes), ear infections, chronic constipation, and eating problems.

Individuals with Williams syndrome can have distinct facial features sometimes described as "elfin" or "pixie-like." While none of these individual facial features are abnormal, the combination of the different features is common for Williams syndrome. Individuals with Williams syndrome have a small upturned nose, a small chin, long upper lip with a wide mouth, small widely spaced teeth, and puffiness around the eyes. As an individual gets older, these facial features become more pronounced.

People with Williams syndrome often have problems with narrowing of their heart and blood vessels. This is

thought to be due to the deletion of the elastin gene and is called elastin arteriopathy. Any artery in the body can be affected, but the most common narrowing is seen in the aorta of the heart. This condition is called supravalvar aortic stenosis (SVAS) and occurs in approximately 75% of individuals with Williams syndrome. The degree of narrowing is variable. If left untreated, it can lead to high blood pressure, heart disease, and heart failure. The blood vessels that lead to the kidney and other organs can also be affected.

Deletions of the elastin gene are also thought to be responsible for the loose joints of some children with Williams syndrome. As individuals with Williams syndrome age, their heel cords and hamstrings tend to tighten, which can lead to a stiff awkward gait and curving of the spine.

Approximately 75% of individuals with Williams syndrome have mild mental retardation. They also have a unique cognitive profile (unique learning abilities and disabilities). This cognitive profile is independent of their IQ. Individuals with Williams syndrome generally have excellent language and memorization skills. They can have extensive vocabularies and may develop a thorough knowledge of a topic that they are interested in. Many individuals are also gifted musicians. Individuals with Williams syndrome have trouble with concepts that rely on visuospatial ability. Because of this, many people with Williams syndrome have trouble with math, writing and drawing.

People with Williams syndrome also often share personality characteristics. They are noted to be very talkative and friendly—sometimes inappropriately—and they can be hyperactive. Another shared personality trait is a generalized anxiety.

Diagnosis

The diagnosis of Williams syndrome is usually made by a physician familiar with Williams syndrome and based upon a physical examination of the individual and a review of his or her medical history. It is often made in infants after a heart problem (usually SVAS) is diagnosed. In children without significant heart problems, the diagnosis may be made after enrollment in school when they are noted to be "slow learners."

While a diagnosis can be made based upon physical examination and medical history, the diagnosis can now be confirmed by a **DNA** test.

Williams syndrome is caused by a deletion of genetic material from the long arm of chromosome 7. A specific technique called fluorescent in situ hybridization testing, or FISH testing, can determine whether there is genetic material missing. A FISH test will be positive (detect a deletion) in over 99% of individuals with Williams syndrome. A negative FISH test for Williams syndrome means that no genetic material is missing from the critical region on chromosome 7q11.

Prenatal testing (testing during pregnancy) for Williams syndrome is possible using the FISH test on DNA sample obtained by chorionic villus sampling (CVS) or by **amniocentesis**. Chorionic villus sampling is a prenatal test that is usually done between 10 and 12 weeks of pregnancy and involves removing a small amount of tissue from the placenta. Amniocentesis is a prenatal test that is usually performed at 16–18 weeks of pregnancy and involves removing a small amount of the amniotic fluid that surrounds the fetus. DNA is obtained from these samples and tested to see if the deletion responsible for Williams syndrome is present. While prenatal testing is possible, it is not routinely performed. Typically, the test is only done if there is a family history of Williams syndrome.

Treatment and management

Because Williams syndrome is a multi-system disorder, the expertise of a number of specialists is required for management of this disorder.

The height and growth of individuals with Williams syndrome should be monitored using special growth curves developed specifically for individuals with Williams syndrome. Individuals who fall off these growth curves should be worked up for possible eating or thyroid disorders.

A cardiologist should evaluate individuals with Williams syndrome yearly. This examination should include measurement of blood pressure in all four limbs and an echocardiogram of the heart. An echocardiogram is a special form of ultrasound that looks at the structure of the heart. Doppler flow studies, which look at how the blood flows into and out of the heart, should also be done. Individuals with supravalvar stenosis may require surgery to fix this condition. The high blood pressure caused by this condition may be treated with medication. Examinations should take place yearly as some of these conditions are progressive and may worsen over time.

Individuals with Williams syndrome should also have a complete neurological examination. In addition, the blood calcium levels of individuals with Williams syndrome should be monitored every two years. High levels of calcium can cause irritability, vomiting, constipations and muscle cramps. An individual found to have a high level of calcium should consult a nutritionist to make sure that their intake of calcium is not higher than 100% of the recommended daily allowance (RDA).

Because vitamin D can increase calcium levels, individuals with Williams syndrome and high calcium should not take multivitamins containing vitamin D. If calcium levels remain high after limiting vitamin D and decreasing dietary intake of calcium, an individual with hypercalcemia should see a nephrologist for further management and to monitor kidney function.

Strabismus (crossed eyes) can be treated by patching or by surgery. Ear infections can be treated with antibiotics and surgical placement of ear tubes.

The developmental differences of individuals with Williams syndrome should be treated with early intervention and special education classes. Specific learning strategies that capitalize on the strengths of individuals with Williams syndrome should be used. Physical, occupational, and speech therapy should be provided. Behavioral counseling and medication may help with behavioral problems such as hyperactivity and anxiety.

Prognosis

The prognosis for individuals with Williams syndrome is highly dependent on the medical complications of a particular individual. Individuals with Williams syndrome who have no heart complications, or very minor ones, have a good prognosis. Good medical care and treatment of potential problems allows most individuals with Williams syndrome to lead a long life. The prognosis for individuals with more serious medical complications such as severe heart disease or hypertension is more guarded. Since the medical conditions associated with Williams syndrome are progressive rather than static, it is very important that individuals with Williams syndrome have yearly medical examinations with a health care provider familiar with Williams syndrome.

The range of abilities among individuals with Williams syndrome is very wide and the ultimate functioning of an individual is dependent on his or her abilities. While individuals with Williams syndrome do well in structured environments such as school, their unique abilities and disabilities do not permit them to do as well in unstructured surroundings. Some individuals with Williams syndrome live independently but most live with their parents or in a supervised setting. Many individuals with Williams syndrome can gain employment in supervised settings and do well at tasks that do not require mathematics or visuospatial abilities. It is important to encourage individuals with Williams syndrome towards independence but to recognize that their friendly and outgoing personalities may lead them into abusive situations.

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Williams Syndrome Foundation. University of California, Irvine, CA 92679-2310. (949)824-7259. <http://www.wsf.org/>.

Kathleen Fergus, MS, CGC

Williams-Beuren syndrome *see* **Willams syndrome**

Wilson disease

Definition

Wilson disease is a rare, inherited disorder that causes excess copper to accumulate in the body. Steadily increasing amounts of copper circulating in the blood are deposited primarily in the brain, liver, kidneys, and the cornea of the eyes.

Description

Under normal conditions, copper that finds its way into the body through the diet is processed within the liver. This processed form of copper is then passed into the gallbladder, along with the other components of bile (a fluid produced by the liver, which enters the small intestine in order to help in digestive processes). When the gallbladder empties its contents into the first part of the small intestine (duodenum), the copper in the bile enters and passes through the intestine with the waste products of digestion. In healthy individuals, copper is then passed out of the body in stool.

In Wilson disease, copper does not pass from the liver into the bile, but rather begins to accumulate within the liver. As copper levels rise in the liver, the damaged organ begins to allow copper to flow into the bloodstream, where it circulates. Copper is then deposited throughout the body, building up primarily in the kid-

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bile—A substance produced by the liver, and concentrated and stored in the gallbladder. Bile contains a number of different substances, including bile salts, cholesterol, and bilirubin.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Ceruloplasmin—A protein circulating in the bloodstream that binds with copper and transports it.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cirrhosis—A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Gallbladder—A small, pear-shaped organ in the upper right hand corner of the abdomen. It is connected by a series of ducts (tube-like channels) to the liver, pancreas, and duodenum (first part of the small intestine). The gallbladder receives bile from the liver, and concentrates and stores it. After a meal, bile is squeezed out of the gallbladder into the intestine, where it aids in digestion of food.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Glucose—One of the two simple sugars, together with galactose, that makes up the protein lactose, found in milk. Glucose is the form of sugar that is usable by the body to generate energy.

Hepatitis—A viral disease characterized by inflammation of the liver cells (hepatocytes). People infected with hepatitis B or hepatitis C virus are at an increased risk for developing liver cancer.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Toxic—Poisonous.

neys, the brain and nervous system, and the eyes. Wilson disease, then, is a disorder of copper poisoning occurring from birth.

Genetic profile

Wilson disease is inherited in an autosomal recessive manner. Autosomal recessive refers to the pattern of **inheritance** in which each parent carries a **gene** for the disease on one of his or her chromosome pairs. When each parent passes on the chromosome with the gene for Wilson disease, the child will be affected with the disease. Both males and females can be affected with Wilson disease. If an individual is a carrier of the Wilson disease gene, they do not have any symptoms of this disease. In order to be affected, an individual must inherit two copies of the gene, one from each parent. Many cases of Wilson disease may not be inherited but occur as a spontaneous mutation in the gene.

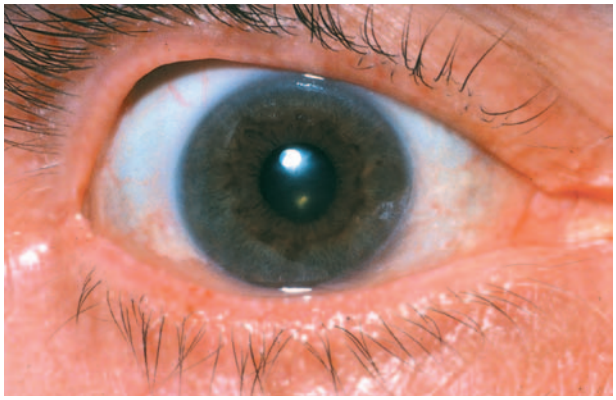
The gene for Wilson disease is located on chromosome 13. The name of the gene is called ATP7B and is thought to be involved in transporting copper. As of 2001, over 70 different mutations of this gene have been identified, making diagnosis by **genetic testing** difficult.

Demographics

Wilson disease affects approximately 1 in 30,000 to 1 in 100,000 individuals and can affect people from many different populations. Approximately 1 in 90 individuals are carriers of the gene for Wilson disease.

Signs and symptoms

Symptoms typically present between the ages of three and 60, with age 17 considered to be the average age a diagnosis is made. About half of all patients



Copper deposits are visible as a ring around the iris in patients with Wilson disease. Copper deposits in other organs as well and must be removed to avoid severe mental and physical development disorders. *(Photo Researchers, Inc.)*

experience their first symptoms in the liver. The illness causes swelling and tenderness of the liver, sometimes with fever, mimicking more common disorders, such as viral hepatitis and infectious mononucleosis. Abnormal levels of circulating liver enzymes reveal that the liver is being seriously damaged. This form of damage is referred to as "fatty degeneration." Without medical intervention, the liver damage will progress to actual cirrhosis. An often-fatal manifestation of liver disease is called fulminant hepatitis. This extremely severe inflammation of the liver (hepatitis) results in jaundice, fluid leaking into the abdomen, low protein circulating in the blood, abnormalities of the blood clotting system, swelling of the brain, and anemia due to the abnormal destruction of red blood cells.

Neurological symptoms are the first to occur in half of all patients due to copper accumulation in the brain and nervous system. The average age of onset for neurological symptoms is 21 years. These symptoms include tremors of the hands, uncontrollable movements of the limbs, stiffness, drooling, difficulty swallowing, difficulty talking, and headache. There is no change in a patient's intelligence.

About one third of all patients with Wilson disease have a variety of psychiatric symptoms as the first signs of the disease. These symptoms include inability to cope, **depression**, irritability, increased anger, and inappropriate behavior. Patients often have trouble completing tasks at work or in school.

Other symptoms that can affect patients with Wilson disease, and may occur before or after a diagnosis has been made, include joint disorders, symptoms of arthritis, and skeletal problems such as **osteoporosis**. Patients have occasionally been affected with kidney stones and abnormal handling of glucose in their body, and women may have menstrual cycle irregularities including temporary stopping of their regular cycle.

Diagnosis

The diagnosis of Wilson disease can be performed relatively easily through several different tests, however, because Wilson disease is so rare, diagnosis is often unfortunately delayed. The tests used to diagnose Wilson disease can be performed on patients who have or have not already shown symptoms of the disease. It is extremely important to make a diagnosis as soon as possible since liver damage can occur before there are any signs of the disease.

An easy way to diagnose Wilson disease is to measure the amount of a glycoprotein found in the blood called ceruloplasmin. Low levels of ceruloplasmin can diagnose the disease in about 80% of affected patients. This procedure is not as effective for women taking birth control pills, pregnant women, or infants less than six months of age.

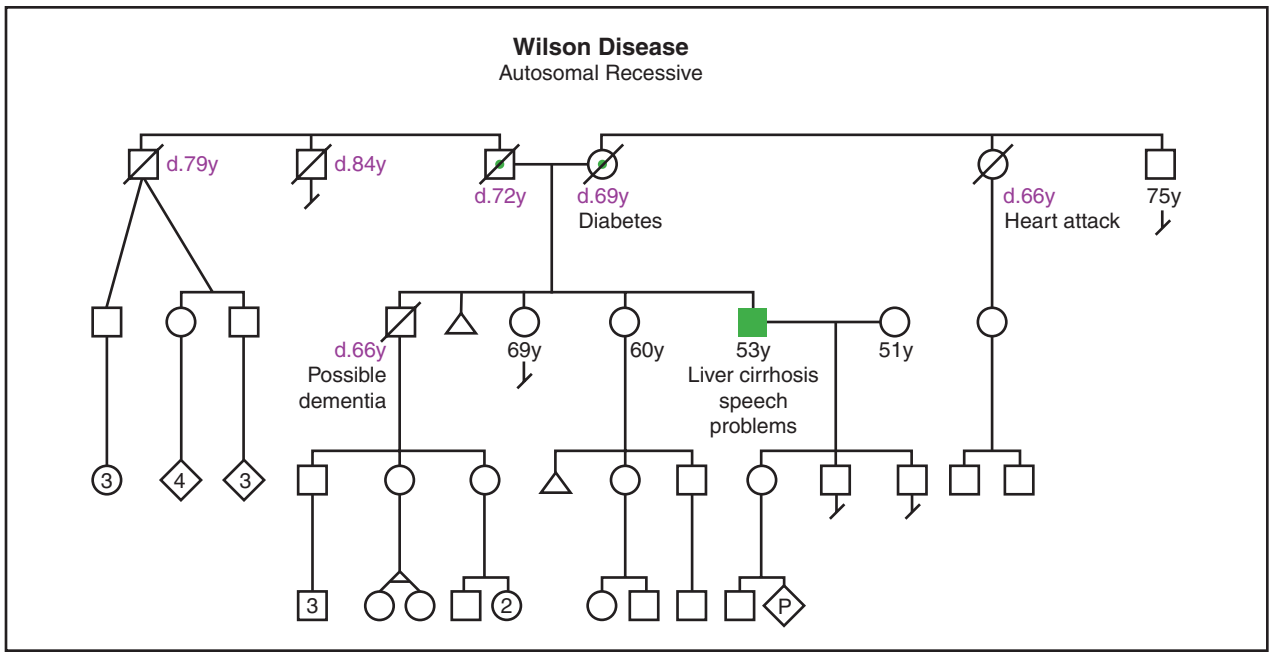
A second test involving an eye examination to detect a characteristic ring of copper deposited in a membrane of the cornea (referred to as Kayser-Fleischer rings) is very easy to perform and is very useful in diagnosing patients who have already exhibited symptoms. This test is not as effective in persons without symptoms. This diagnostic test cannot be used by itself to make a diagnosis because some patients with liver disease but not Wilson disease will test positive.

A third test for diagnosing Wilson disease involves measuring the amount of copper in the liver. This can be accomplished by sampling a portion of the liver in a procedure called a biopsy. This is one of the most effective ways to diagnose Wilson disease, however, the procedure itself is more difficult to perform than the others.

Other tests are also useful, for example, measuring the amount of copper passed into the urine daily (high in Wilson disease). Another lab test measures the ability of a patient's ceruloplasmin to bind with a form of copper (decreased in Wilson disease). And finally, as discussed under genetic profile, some patients can be diagnosed through a **DNA** test to determine whether or not they carry two genes for Wilson disease. This test does not always prove to be useful in certain patients and is most useful when testing the brothers and sisters of affected patients.

Treatment and management

Treatment involves life-long administration of either D-penicillamine or trientine hydrochloride. Both of these



(Gale Group)

drugs remove copper deposits throughout the body by binding to the copper which is removed from the body in urine. Zinc acetate and a low copper diet are other ways to treat Wilson disease.

Penicillamine has a number of serious side effects:

- joint pain
- neurological problems
- systemic lupus erythematosus
- decreased production of all blood elements
- interference with clotting
- allergic reactions

Careful monitoring is necessary. When patients have side effects from penicillamine, the dose can sometimes be lowered to an effective level that causes fewer difficulties. Alternatively, steroid medications may be required to reduce certain sensitivity reactions. Trientine has fewer potential side effects, but must still be carefully monitored.

Treatment with zinc is also an effective way to remove excess copper from the body. Zinc is a metal that works to block copper absorption and bind copper in the intestinal cells until it is all released into the stool approximately one week later. The benefit of treatment with zinc is that there are no toxic side effects, however, the zinc is a slower acting agent than the other drugs. It takes four to eight months for the zinc to be effective in reducing the overall amount of copper in the body.

Finally, patients with Wilson disease are encouraged to follow a diet low in copper, with an average copper intake of 1.0 mg/day. Foods to avoid for their high levels of copper include liver and shellfish. Patients are also instructed to monitor their drinking water for excess levels of copper and drink distilled water instead.

Prognosis

Without treatment, Wilson disease is always fatal. With treatment, symptoms may continue to worsen for the first six to eight weeks. After this time, definite improvement should start to be seen. However, it may take several years (two to five) of treatment to reach maximal benefit to the brain and liver. Even then, many patients are not returned to their original level of functioning. Patients with Wilson disease need to maintain some sort of anticopper treatment for the rest of their lives in order to prevent copper levels from rising in the body. Interruptions in treatment can result in a relapse of the disease which is not reversible, and can ultimately lead to death.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

Wilson's Disease Association. 4 Navaho Dr., Brookfield, CT 06804. (800) 399-0266.

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Katherine S. Hunt, MS

Wiskott-Aldrich syndrome

Definition

Wiskott-Aldrich syndrome (WAS) is a rare inherited disorder marked by a low level of blood platelets, eczema, recurrent infections, and a high risk of leukemia or lymph node tumors.

Description

WAS was named for the two physicians who first reported the disorder. In 1937, Dr. A. Wiskott, a physician working in Munich, described two affected boys of German ancestry who had repeated infections, a skin rash, and poor blood-clotting ability. Nearly twenty years later, Dr. R.A. Aldrich reported similar symptoms in members of an American family of Dutch ancestry.

The syndrome is caused by a defect (mutation) in a specific **gene** called the WAS gene that normally codes for the protein named Wiskott-Aldrich Syndrome Protein (WASP). This vital protein is a component of cells that are important in the body's defense against infection (lymphocytes). The same protein also functions in the cells that help prevent bleeding (platelets). A less severe form of the disease, X-linked thrombocytopenia, affects mainly the platelets.

Genetic profile

WAS is inherited as an X-linked genetic disorder and will therefore only affect males. The gene responsible for WAS is located on the short arm of the X chromosome. Since males have only one X chromosome, they only have one copy of the gene. If that copy carries the abnormal gene, they will have WAS. In contrast, females have two X **chromosomes**. They will have a normal copy of the gene on one chromosome even if an abnormal gene is on the other because the abnormal gene is very rare. The normal copy on one X chromosome is usually sufficient to prevent females from having WAS. However, women who have one abnormal copy of the WAS gene are designated as carriers. While they will not have WAS, they have a 50% risk of passing the gene to each of their sons, who would then have WAS. Carrier females also have a 50% risk of passing the defective copy of the gene to their daughters, who then become carriers.

Researchers identified the gene for WAS in 1994 and pinpointed its location on the short arm of the X chromosome (Xp11.22-p11.23). As of 2000, over 100 different mutations have been found in the gene among WAS patients. The fact that there are many mutations may explain some of the variability of symptoms among boys with WAS. However, even within the same family, affected individuals with the identical WAS **gene mutation** may have different degrees of severity of the disease. The mild form, X-linked thrombocytopenia, is also caused by mutations in this same gene.

Demographics

The WAS syndrome affects one in every 250,000 male children and occurs worldwide. In the year 2000, scientists estimated that about 500 Americans have WAS.

Signs and symptoms

Increased susceptibility to infections, eczema, and excessive bleeding are the hallmarks of WAS, although the symptoms can vary signficantly from one patient to another. The immune system of patients with WAS produces too few B and T cells. B cells are the cells in the body that make antibodies. There are many types of T cells. Both B and T cells are needed to defend the body against infection. Because both types of cells are affected, WAS patients are subject to repeated infections from bacteria, fungi, and viruses. Ear infections, meningitis, and pneumonia are common in boys with WAS.

WAS patients also have thrombocytopenia, a decreased number of platelets. Platelets are the specialized blood cells that help to form blood clots and prevent uncontrolled bleeding. The platelets may also be smaller

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Eczema—Inflammation of the skin with redness and other variable signs such as crusts, watery discharge, and itching.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

Prenatal diagnosis—The determination of whether a fetus possesses a disease or disorder while it is still in the womb.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

Thrombocytopenia—A persistent decrease in the number of blood platelets, usually associated with hemorrhaging.

X-linked—Located on the X chromosome, one of the sex chromosomes. X-linked genes follow a characteristic pattern of inheritance from one generation to the next.

than normal. Some of the earliest symptoms of the syndrome are hemorrhage from circumcision, bloody diarrhea, and a tendency to bruise very easily.

Anemia and an enlarged spleen (splenomegaly) are seen in some patients. About 10% of patients develop malignancies, usually leukemia or tumors in the lymph nodes (non-Hodgkin's lymphoma).

Diagnosis

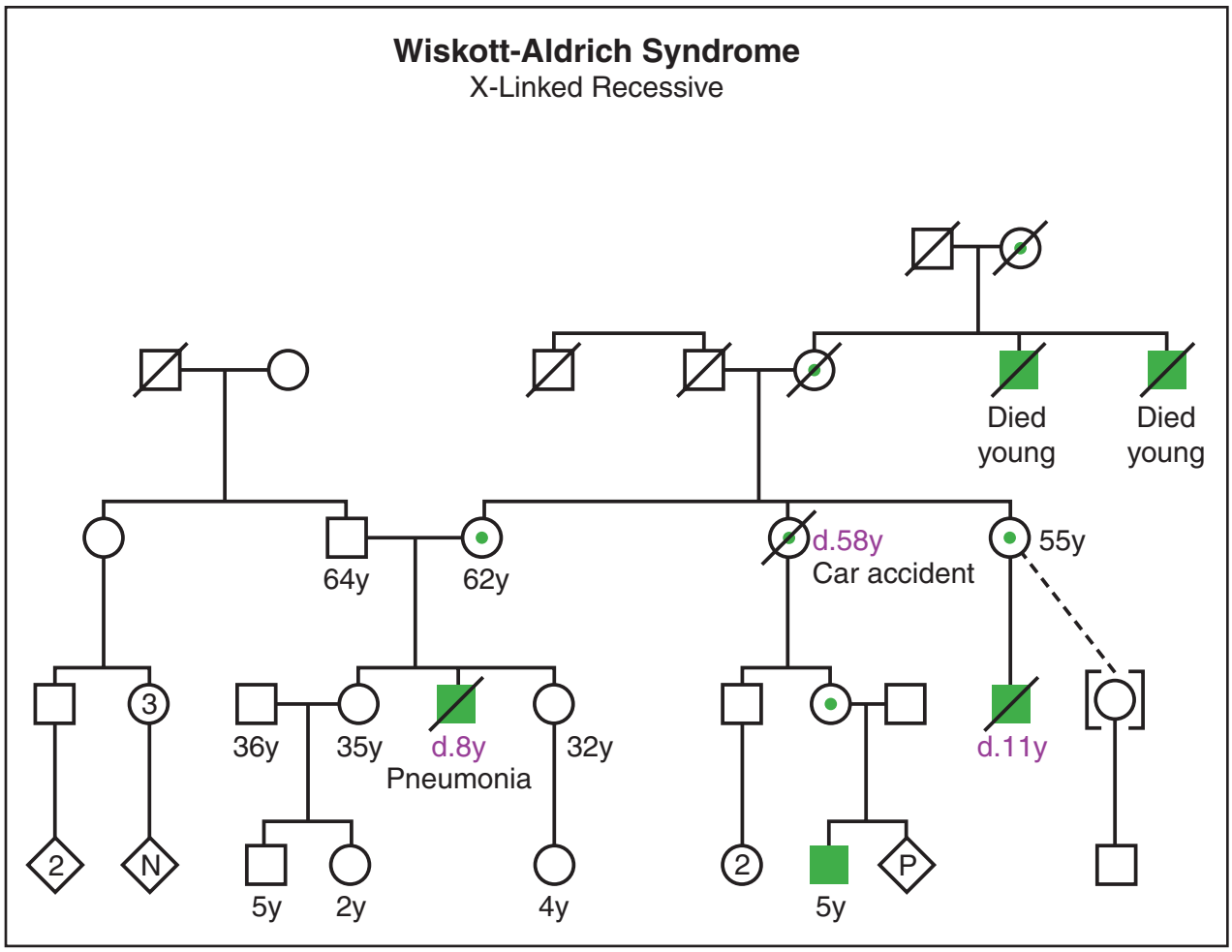
The diagnosis of WAS is usually suspected in male infants who have excessive bleeding, eczema, and frequent bacterial or viral infections. Special blood tests can then be ordered to confirm WAS. The blood of patients with Wiskott-Aldrich will show a low platelet count and a weak immune (antibody) response. It is also possible to confirm the diagnosis by obtaining a small sample of the patient's blood and analyzing the **DNA** for a mutation in the WAS gene. Knowledge of the exact mutation combined with information about how much WAS protein the defective gene can produce may help predict how severe a form of the disease an individual will have.

Carrier testing

If the specific WAS gene mutation is identified in an affected child, that child's mother can then be tested to confirm that she carries the gene. Other members of the mother's family may also want to consider testing to find out if they carry the same gene mutation. The first step in studying other family members is for a geneticist or genetic counselor to obtain a detailed family history and construct a pedigree (family tree) to determine which family members should be offered testing.

Prenatal diagnosis

In families in which there has been one child born with WAS, prenatal testing should be offered in subsequent pregnancies. There is a 50% chance with each subsequent pregnancy that the mother, who is a carrier, will



(Gale Group)

transmit the abnormal copy of the gene to her baby. The key is to first identify the particular WAS gene mutation in the child with WAS. Then, early in a pregnancy, cells can be obtained from the developing fetus by chorionic villus sampling or **amniocentesis**, and checked for the same mutation. Women who carry the abnormal WAS gene and are considering prenatal diagnosis should discuss the risks and benefits of this type of testing with a geneticist or genetic counselor.

Treatment and management

Standard treatments for individuals with WAS include antibiotics for infections and platelet transfusions to limit bleeding. Immune globulin is given to strengthen the individual's immune system. Eczema can be treated with corticosteroid creams applied directly to the skin. The spleen is sometimes removed to reduce the risk of bleeding. In individuals with WAS, however, removal of the spleen also increases the risk of infection unless antibiotics are given to prevent infections. About 50% of individuals with WAS are helped by treatment with transfer factor, which is a substance derived from the T cells of a healthy person. Transfer factor is given to improve both blood clotting and immune functions. Bone marrow transplantation has been successful in a number of cases. It has been most successful in boys under five years of age when the donor is a sibling whose tissue type closely matches that of the individual with WAS. As of 2000, attempts were also being made to treat individuals with WAS with umbilical cord blood from unrelated newborns in cases when the individual diagnosed with WAS has no matched sibling donor.

Prognosis

The prognosis for males diagnosed with Wiskott-Adrich syndrome is poor. The average individual lives about four years; those who survive into adolescence often develop **cancer**. Death usually occurs from severe

bleeding or overwhelming infection in the first few years of life.

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Sallie Boineau Freeman, PhD

Wolf-Hirschhorn syndrome

Definition

Wolf-Hirschhorn syndrome (WHS) refers to a condition that is caused by a missing part (deletion) of the short arm of chromosome 4. This missing genetic material results in severe developmental retardation, a characteristic facial appearance, and may include a variety of other birth defects.

Description

This syndrome was reported in 1965 in published reports by Wolf and Hirschhorn, who described that the characteristics of the syndrome were associated with a deletion of part of the short arm of chromosome 4. The short arm of a chromosome is called the "p" arm. Thus, this syndrome is also known as 4p-syndrome or deletion 4p syndrome, and occasionally as Wolf syndrome.

A normal human **karyotype** consists of 23 pairs of **chromosomes**. Each pair is numbered 1 through 22 and the 23rd pair are the sex chromosomes. On each chromosome are hundreds of genes that determine how our bodies look and function. WHS is a contiguous **gene** syndrome. A contiguous gene syndrome occurs when a chromosome is either missing material (deletion) or has extra material (duplication) of several genes in the same region of the chromosome. Each time that the deletion or duplication of those genes occur, they cause specific characteristics that come to be known as a particular syndrome. This is in contrast to having just one particular gene cause a syndrome. Some patients who have WHS may have a small deletion on 4p, while others may be missing up to half of 4p. For this reason, some individuals have a less severe case of WHS than others do. The band 4p16.3 needs to be deleted in order for an individual to have full expression of WHS.

WHS frequently presents prenatally with slow growth (intrauterine growth retardation). Some infants with WHS can be stillborn or die shortly after birth. As many as 1/3 of reported patients have died in the first year of life. Individuals with WHS have been described as having a characteristic facial appearance likened to a "Greek Helmet facies." This can be described as having a small head size (microcephaly), eyes spaced widely apart (ocular hypertelorism), downturned mouth, short upper lip and short groove between the upper lip and nose (philtrum) or bilateral cleft lip and small chin (micrognathia).

These children have severe developmental retardation. Other significant problems can include heart defects, cleft lip and/or palate, hearing impairment, and eye problems. Most children who have WHS have seizures (approximately 90%). Seizures are one of the major health concerns in children with WHS. These seizures begin between 5 and 23 months of age, however approximately 50% of the individuals stop having seizures between age 3 and 11. Sleeping problems are also common in children who have WHS. Although it seems that most of the literature focuses on children who have WHS, there are adults who have WHS.

Genetic profile

Frequently, with routine chromosome analysis, it is possible to identify that the short arm of chromosome 4 is missing some genetic material. The size of the missing material may vary from patient to patient. At times, the deletion is so small that it cannot be detected by routine chromosome analysis. If a patient is suspected to have WHS and an obvious deletion is not detected by routine chromosome analysis, more detailed studies, including fluorescent in situ hybridization, are warranted and may identify the missing genetic material. WHS may also present as mosaicism. Mosaicism for 4p-syndrome means that the

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

In vitro fertilization—Process by which a woman has her eggs surgically removed and fertilized in the laboratory. The developing embryos can then be transferred to her uterus to hopefully achieve a pregnancy.

individual has some cells that have normal number 4 chromosomes and other cells that are missing some of the genetic material from 4p.

Approximately 85–90% of cases of WHS occur as the result of a new deletion in the affected individual. This is also known as a *de novo* deletion and simply means that the affected individual's parents did not have any chromosome arrangement that led to the deletion. In this case, the chance for recurrence in future pregnancies of a couple whom has an affected child is not increased. In the remaining 10–15% of cases, one of the parents of the affected individual carries a balanced translocation. A balanced translocation is a rearrangement in the individual's chromosomes that causes that individual no problems since they have all the necessary genetic material that they need. However, when they produce eggs or sperm, the eggs or sperm may end up with an unbalanced arrangement and could lead to the conception of a child who has missing or extra genetic material. This could lead to miscarriage or to the birth of a child with conditions, such as WHS.

When a parent is identified as being a carrier of a balanced translocation, with each pregnancy they have an increased chance for having a child with an unbalanced chromosome arrangement. The chance of this is determined by the individual's specific translocation, how it was identified, and which parent is the carrier of the translocation. **Genetic counseling** should be offered for any family in which a child is diagnosed to have WHS. Other family members should also be offered counseling and chromosome analysis to determine if they are carriers of a balanced translocation.

Demographics

The incidence of this condition is rare and estimated to be approximately one in 50,000 births. However, as with many genetic conditions, the condition may be misdiagnosed or may not be diagnosed in all individuals who are affected, especially if the condition results in pregnancy loss or loss in the early newborn period. It has been estimated that approximately 35% of individuals who have WHS die within the first two years of life. Also, with the advent of prenatal diagnosis, some fetuses with ultrasound abnormalities may be detected prenatally and the parents may elect to terminate the pregnancy. Approximately two-thirds of reported cases have been females.

Signs and symptoms

It is important to remember that each individual who may have a particular genetic syndrome is a unique individual. Therefore, all individuals with WHS do not have all of the same signs and symptoms. The most important reason for diagnosing an individual with a syndrome is not to put a label on that person. The reason for a diagnosis is so that predictions can be made to determine the needs of that person, based on the history available from other individuals affected with the same condition.

Signs and symptoms that can be associated with WHS include:

- slow growth before birth
- slow growth after birth (postnatal growth deficiency)
- small head size (microcephaly)
- weak cry in infancy
- poor muscle tone (hypotonia)
- seizures
- severe developmental retardation
- severe retardation of motor skills
- crossed eyes (strabismus)
- widely spaced eyes (hypertelorism)

- droopy eyelids (ptosis)
- skin folds in the corner of the eyes (epicanthal folds)
- cleft lip and/or palate
- short upper lip and philtrum
- small chin (micrognathia)
- asymmetry of the skull (cranial asymmetry)
- skin tag or pit in front of the ear (preauricular tag or pit)
- downturned mouth
- prominent triangular area of the forehead (glabella)
- scalp defects on the center of the back of the head
- underdeveloped fingerprints (dermal ridges)
- a single crease across the palm of the hands (simian crease)
- misaligned bones in the front part of the foot/clubfoot (talipes equinovarus)
- turned up fingernails
- urinary opening on the underside of the penis (Hypospadias)
- undescended testicles (cryptorchidism)
- dimple at the base of the spine
- heart defects
- curvature of the spine (scoliosis)
- underdeveloped bones of the hands and pelvis

Diagnosis

When WHS is suspected, chromosome analysis should be performed and the laboratory should be informed as to what syndrome is suspected. This ensures that the laboratory carefully looks at chromosome 4 and if the deletion is not visible, then fluorescent in situ hybridization (FISH) can be done specifically for the critical 4p16.3 region of chromosome 4. FISH analysis is a procedure that is used in the laboratory to identify pieces of genetic material that are too small to see by looking at the chromosome under the microscope. Instead, **DNA** that is specific to a particular area of a chromosome is fluorescently labeled, so that it is visible under the microscope. This labeled DNA is then added to the sample and allowed to attach itself to the particular piece of DNA in question. This enables the laboratory technician to then look under the microscope for the fluorescent spot on the chromosome and identify extra or missing pieces of DNA that are too small to see by just looking at the chromosome alone. With this procedure, those individuals who have deletions so small that they cannot be detected by routine chromosome analysis may be able to have the deletion detected by FISH.

Interestingly, there is a syndrome called Pitt-Rogers-Danks syndrome (PRDS) that has been reported to have similar characteristics to WHS. Several individuals who have initially been diagnosed with PRDS, subsequently had FISH analysis that detected a deletion of 4p, and thus the individuals were reclassified as having WHS. Some feel that PRDS is actually WHS without obvious deletions of 4p.

When a couple has had a child diagnosed with WHS, and a member of that couple carries a balanced translocation, genetic counseling should be offered to discuss reproductive options. One option is choosing sperm or egg donation so that the parent who has the translocation does not pass unbalanced genetic material on to his or her child. Another option is preimplantation genetic diagnosis. Preimplantation genetic diagnosis is a very complex process that involves in vitro fertilization and diagnosing the embryos before they are placed into the mother's uterus. Thus, only unaffected embryos are transferred to the uterus. Lastly, the options of CVS and **amniocentesis** for prenatal diagnosis should be discussed. All of these options have allowed couples who have balanced translocations, to realize the dream of having more children when the fear of having another affected child may have otherwise stopped them from choosing to add to their families.

If ultrasound examination reveals findings consistent with the possibility of WHS in a family with no history of WHS, genetic counseling and prenatal diagnosis should be offered. These ultrasound findings may include heart defects, microcephaly, agenesis of the corpus collosum (missing a specific part of the brain), micrognathia, **cleft lip and palate**, a hole in the diaphragm (diaphragmatic hernia), hypospadius, and clubbed feet. Keep in mind that these findings can also be consistent with other genetic syndromes.

Treatment and management

There is no treatment for the underlying condition of WHS. Treatment and management for patients who have WHS are specific to each individual. For example, some individuals with WHS may have heart defects or a cleft lip and/or palate that may require surgery, while others may not. Therefore, there is no specific treatment for individuals who have WHS, rather, the treatment and management is geared toward that particular individual's needs and is likely to include several medical specialists. Information about patients who have WHS has been compiled and provides a comprehensive look into the natural history of this condition. It also allows the following management guidelines to be recommended. The collection of this

information has shown that many of these individuals may achieve more development than was previously believed possible.

The following management recommendations have been made by Drs. Battaglia and Carey:

- Feeding problems should be addressed and may require intervention such as placement of a gastrostomy tube.
- Characterization of seizures is important and treatment with antiepileptic medications such as valproic acid should be investigated and may help control the seizure activity in many individuals.
- Skeletal abnormalities such as **clubfoot** should be addressed and treatment should be considered. It should not be assumed that a clubfoot does not need to be addressed because the child will never walk. Children with WHS have learned to walk unassisted.
- As approximately 30% of individuals may have **congenital heart defects**, the heart should be examined. Usually, the heart lesions are not severe and may be repaired easily or may not even require surgery.
- Hearing loss may occur and because some children are able to learn to talk in short sentences, they should be screened for hearing problems.
- Eye abnormalities may be present and thus an ophthalmology exam should be performed to rule out any eye problems, even if no obvious signs are present.
- In regards to the development of patients with WHS, it is suggested that individuals participate in personal development programs to assist with social skills and occupational therapy for motor skills.

Prognosis

Infants with WHS may be stillborn or die in the newborn period and prognosis during the newborn period depends upon what birth defects are present. It has been estimated that approximately 35% of individuals who have WHS die within the first two years of life. Many individuals with WHS survive to adulthood. Universally, children with WHS have severe or profound developmental retardation, however, there are many affected individuals who are able to walk and some that are able to talk in short sentences. It is evident that many patients seem to proceed farther than was previously thought possible. The actual lifespan for individuals who have WHS is unknown, although there are several individuals who have WHS who are in their 20s–40s.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

4p- Support Group. <http://www.4p-supportgroup.org>.

Renee A. Laux, MS

Wolman disease

Definition

Wolman disease is a rare inherited defect in the body's metabolism of fats (lipids).

Description

Wolman disease, also known as lysosomal acid lipase disease, is a lethal genetic disorder caused by the lack of the enzyme lysosomal acid lipase. Lysosomal acid lipase is a cellular enzyme widespread throughout the body. It is important in the breakdown of certain body lipids called triglycerides and cholesteryl esters. Individuals without active enzyme accumulate abnormally large amounts of these lipids in their cells. This build-up interferes with the normal metabolic functions of the cells and leads to severe neurological and physical symptoms and early death. A milder disease, cholesteryl ester storage disease (CESD), is caused by mutations in the same **gene**, but affected individuals may not show symptoms until adulthood.

Genetic profile

Inheritance pattern

Wolman disease is an autosomal recessive disorder affecting both males and females. In individuals with this disorder, both copies of the gene that codes for lysosomal

KEY TERMS

Adrenal gland—A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Heterozygote—Having two different versions of the same gene.

Lysosomal—Pertaining to the lysosomes, special parts (organelles) of cells that contain a number of enzymes important in the breakdown of large molecules such as proteins and fats.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

acid lipase are abnormal. Both parents of an affected child have one abnormal copy of the gene, but usually do not show symptoms because they also have one normal copy. The normal copy provides approximately 50% of the usual enzyme activity, a level adequate for the body's needs. Individuals with one abnormal copy of the gene and 50% enzyme activity are said to be carriers or heterozygotes. Because both parents of a child with Wolman disease are carriers, they have a 25% risk in each subsequent pregnancy of having another child who is affected with the same disorder.

Gene location

The gene for acid lipase is located on the long arm of chromosome 10 at 10q23.2-q23.3. A number of different types of mutations in this gene, all resulting in a lack of enzyme function, have been identified in patients diagnosed with Wolman disease. These include deletions of small portions of the gene, as well as changes in specific nucleotides, the building blocks of the gene. The different mutations may explain why symptoms vary from one individual to another. However, the presence of variability in symptoms even among siblings who have inherited the same mutations from their parents, suggests there may be other, as yet unknown, genetic or environmental factors that affect the severity of the disease. Milder forms, such as the related disorder CESD, appear to be associated with gene mutations that result in only partial loss of enzyme function.

Demographics

In the general population, Wolman disease is exceedingly rare, with approximately 50 or fewer well-described cases to date (2000). CESD is thought to be more common. Individuals with Wolman disease have been reported in various parts of the world including Western Europe, North America, Iraq, Iran, Israel, China, and Japan.

Signs and symptoms

Symptoms of Wolman disease appear in the first few weeks of life. Forceful vomiting and distention of the abdomen usually alert parents to a problem. Other

general symptoms in the early stages of this disease are watery diarrhea or fat in the stools, fever, and a yellow tint to the skin (jaundice). Medical examination reveals massive enlargement of the liver and spleen (hepatosplenomegaly) due to a build-up of fats that cannot be broken down. Other common findings are severe anemia, calcium deposits in the adrenal glands, and a general decline in mental development.

Diagnosis

Diagnosis can be difficult because there are no general laboratory tests that point specifically to Wolman disease. Infants with hepatosplenomegaly and evidence of malnutrition should have a careful neurological examination and x rays of the abdomen to check for calcium deposits in the adrenal glands. If Wolman disease is suspected on the basis of these tests, acid lipase activity can be measured in the laboratory using white blood cells or skin cells. An absence of acid lipase activity confirms the diagnosis.

Carrier testing

Individuals suspected of being a carrier of Wolman disease can be confirmed by measuring acid lipase activity in their white blood cells. Carriers will typically demonstrate 50% of normal enzyme activity.

Mutation detection

Specific **DNA** tests that check for changes in the normal sequence of nucleotides in the acid lipase gene can usually detect the particular **gene mutation** in an affected individual or carrier. This type of test is only available in a few, very specialized DNA laboratories.

Prenatal diagnosis

Couples who have had one child with Wolman disease may be offered prenatal testing in future pregnancies. Prenatal testing is accomplished by measuring acid lipase activity either in cells from a chorionic villus sampling (CVS) at about 10–12 weeks of pregnancy or in amniotic fluid cells obtained by **amniocentesis** between the sixteenth and eighteenth weeks of pregnancy. Alternatively, if specific gene mutations have been identified in parents because they have already had a affected child, fetal DNA from chorionic villus cells or amniotic fluid cells can be studied to look for these same mutations in the fetus. Carrier couples who are considering prenatal diagnosis should discuss the risks and benefits of this type of testing with a geneticist or genetic counselor.

Treatment and management

There is no specific treatment for Wolman disease. There have been attempts to treat the milder CESD with low-fat diets and cholesterol-lowering drugs, and there has been at least one report of a liver transplant in a patient with CESD. Replacement of the missing enzyme has not been reported.

Prognosis

Infants diagnosed with Wolman disease usually die by six months of age.

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National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

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Sallie Boineau Freeman, PhD

X

Xeroderma pigmentosum

Definition

Xeroderma pigmentosum is a rare inherited genetic disease. People with this condition develop skin and eye cancers at young ages because their **DNA** is extremely susceptible to damage caused by ultraviolet radiation. Xeroderma (dry, scaly skin) and pigmentosum (freckling and abnormal skin coloring) refer to changes that occur after exposure to sunlight or other ultraviolet radiation.

Description

Xeroderma pigmentosum refers to a group of similar conditions. Each subgroup is designated by a letter or a roman numeral. Xeroderma pigmentosum is also often abbreviated XP. XP A and XP I are the same, as are XP B and XP II, XP C and XP III, etc. There are seven types of xeroderma pigmentosum designated A–G or I–VII. An eighth type of XP is called the "variant" type. XP VIII/XP H was once a separate subgroup; now it known to be part of XP D/XP IV.

Each of the eight types of xeroderma pigmentosum has its own DNA defect. However, each section of DNA affected is involved in the same process. These defects affect the body's ability to repair DNA damage, especially DNA damage to the skin caused by exposure to ultraviolet radiation. Sunlight is the most common source of ultraviolet radiation. Everyone's DNA is damaged when it is exposed to sunlight. However, the body has complex and very effective methods to repair the DNA damage. This repair mechanism does not work properly in people with xeroderma pigmentosum. They quickly accumulate damage to their DNA if they are exposed to ultraviolet radiation. Cumulative DNA damage leads to **cancer**, especially of the skin and the eyes.

DeSanctis-Cacchione syndrome refers to the combination of xeroderma pigmentosum along with mental retardation, short stature, and other symptoms. Trichothiodystrophy (TTD) is sometimes caused by the same DNA change that causes XP D, and rarely XP B. People with TTD also have brittle hair and nails, and physical and mental retardation.

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Cancer cells—Have characteristics that distinguish them from normal cells and non-cancerous cells; they are threatening, harmful, and resistant to treatment

Carcinoma—Any cancer that arises in the epithelium, the tissue that lines the external and internal organs of the body.

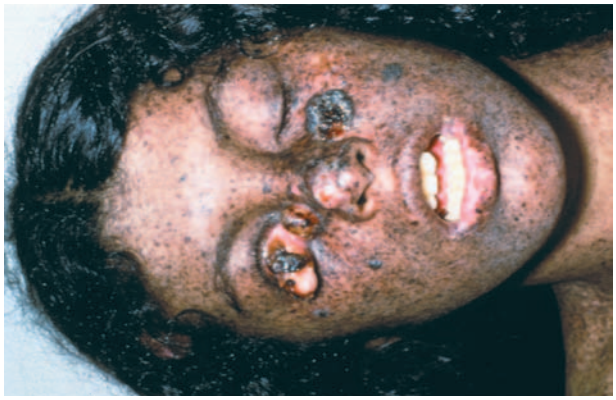
Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

Genetic profile

Xeroderma pigmentosum is inherited as an autosomal recessive condition. Everyone inherits one set of



This woman has a severe case of xeroderma pigmentosum. Her right eye is affected, as well as her left cheek. *(Custom Medical Stock Photo, Inc.)*

genetic material from each parent. People with xeroderma pigmentosum inherited one non-functional XP **gene** from each parent. Their parents have one normal gene and one abnormal gene (of that particular pair); they are called "carriers." Carriers do not have the autosomal recessive conditions because the normal gene in the pair protects them. Two carrier parents have a one in four chance with each pregnancy to have an affected child. A person with xeroderma pigmentosum will have an affected child only if the child's other parent is a carrier or is affected with XP.

The genetics of xeroderma pigmentosum are a bit complicated. The genetic defect in seven of the subgroups has been identified. Each subgroup (A–G) has its own abnormal gene. Each person with xeroderma pigmentosum has a particular subtype, which is associated with one specific abnormal gene. For example, a person with XP type A has no normal XP A gene but does *not* have XP type B and does *not* have the abnormal genes associated with XP type B. The genes for types A, B, C, D, E, F, and G are on **chromosomes** 9, 2, 3, 19, 11, 16, and 13. If two people with different forms of xeroderma pigmentosum had a child, the child would not have xeroderma pigmentosum. But if two people with the same type of xeroderma pigmentosum mated, all of their children would also have xeroderma pigmentosum.

This discussion involves two different types of DNA changes. The first DNA change is the change that the person with xeroderma pigmentosum inherits from both parents. This change (mutation) affects the repair enzymes and is present in every cell in his or her body. The second type of change discussed is additional DNA mutations that result from exposure to ultraviolet radiation. Since the skin and eyes are commonly exposed to ultraviolet radiation that damages DNA and since the body's repair system is not working, people with this condition have a high rate of mutation in the exposed organs. These mutations often manifest themselves as cancers—abnormal, uncontrolled growths. Thus, it is the combination of genetic defect and environmental exposure that causes the manifestations of this disease. The first DNA change would not be nearly as problematic if it did not predispose the person with it to accumulate many additional DNA mutations.

Demographics

Xeroderma pigmentosum occurs in every ethnic group. It occurs equally in men and women. Approximately 1 in 250,000 people in the United States have xeroderma pigmentosum. The most common types are A, C, D, and the variant type.

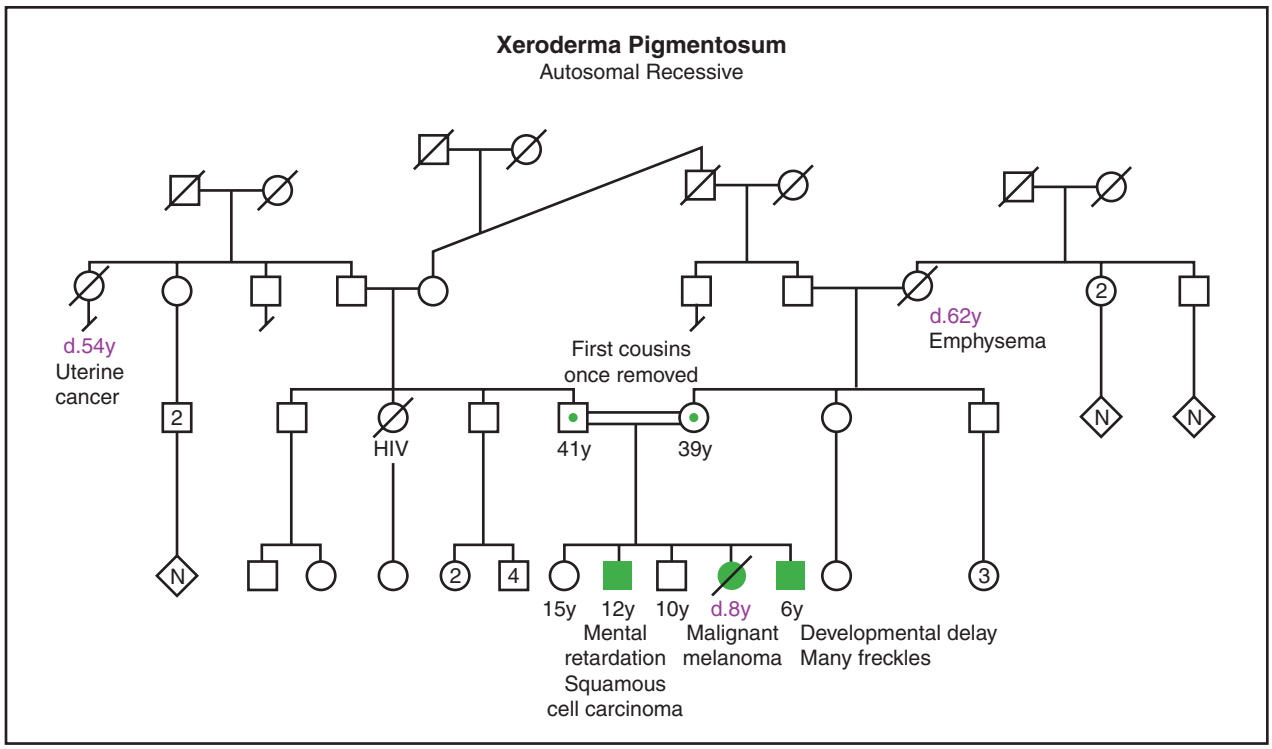
Signs and symptoms

People with xeroderma pigmentosum have photosensitive skin. This means that their skin is hypersensitive to the effects of sunlight. Development of cancer at a young age is the most serious consequence. The eyes are also affected. Some people with xeroderma pigmentosum are affected intellectually, but not all. The symptoms a person will have are somewhat predictable based on which mutation he or she has.

Cutaneous symptoms

Skin manifestations usually begin in infancy. Early effects of skin exposure to minimal ultraviolet radiation include acute sunburn, blistering, freckles, increased or decreased pigment, birthmark-like spots, inflammation, dryness, and rough spots. The face, hands, neck, and arms are more severely affected because of increased sun exposure. Multiple scars may develop. The skin is normal at birth.

The average age at which people with xeroderma pigmentosum develop the first skin cancer is eight years. The risk to develop skin cancer is increased 1,000 times over the risk of the general population. A cell accumulates multiple abnormalities in its transition from a normal cell to a cancer cell. Cancers that occur frequently in people with xeroderma pigmentosum include squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. Basal cell cancers are malignant and, if untreated, are characterized by relentless local invasion, but not metastasis elsewhere in the body. Squamous cell cancers are also malignant and, like basal cell carcinomas, tend to be local, although they are occasionally capable of metastasis. Malignant melanoma, as the name implies, is also malignant, but is much more agressive than either basal



(Gale Group)

cell or squamous cell cancers of the skin. It is especially threatening because if not diagosed and treated early, it commonly will spread to internal organs and can be fatal. Cancer may occur on the eyes, lips, and tongue.

Ocular symptoms

Most people with xeroderma pigmentosum also have extremely light sensitive eyes. Their eyes easily become irritated, red, and swollen. Abnormal growths may appear. Cataracts may occur at an unusually young age.

Other symptoms

The other symptoms associated with xeroderma pigmentosum are variable. Many people who are affected have only eye and skin manifestations. Mental deterioration may occur; when it does, it usually worsens over time. Neurological symptoms are not believed to be associated with sun exposure. Some people have one or a combination of: deafness, poor reflexes, lower intelligence, or spasticity (in addition to ocular and cutaneous symptoms).

Diagnosis

Xeroderma pigmentosum may be suspected based on a person's history of skin changes that occurred after minimal exposure to sunlight. The diagnosis is confirmed by a blood test or a skin test. The skin or blood cells are sent to a specialty laboratory. Studies are performed to determine whether the cells are hypersensitive to ultraviolet radiation. Scientists may examine whether abnormal changes can be seen in the chromosomes. The type of xeroderma pigmentosum may be determined by genetic studies or other specialized studies.

Genetic testing for xeroderma pigmentosum is complicated because there are eight different genes involved. Genetic tests are usually very specific, looking for a change in one gene. To confirm a diagnosis of xeroderma pigmentosum by DNA testing, scientists must look for multiple changes in eight different genes.

Prenatal diagnosis may be possible, especially if genetic studies have already been performed on an affected sibling and the parents.

Treatment and management

The only treatment for xeroderma pigmentosum is avoiding harmful exposure to ultraviolet radiation and treating/removing growths as they occur. The DNA damage caused by exposure to ultraviolet light accumulates over time and the resulting DNA damage is irreversible.

Life is changed dramatically when a family member has xeroderma pigmentosum. Extreme measures must be

taken to completely avoid exposure to the sun. Preventative measures include: sunglasses, tightly woven long-sleeved clothing, wide brim hats, sunblock, and protective window coverings (at home, in the car, and at school). Children do not play outside during the day. All sources of ultraviolet radiation are avoided, even exposure to certain light bulbs. These precautions are critical to survival. Levels of ultraviolet radiation at home and at school can be measured with special instruments. Abnormal skin growths and other symptoms are treated/removed as they arise. Regular visits are made to the eye doctor, dermatologist, and neurologist. Often psychosocial support is also helpful.

Treatments that would deliver DNA repair proteins into the skin of affected patients are under investigation. Some people with xeroderma pigmentosum may be offered other types of medication, like isotretinoin. The dermatologist weighs the benefit of prescribing a medication against the side effects associated with that medication.

Because our bodies have different mechanisms for fixing different forms of DNA damage, people with xeroderma pigmentosum are most susceptible to DNA damage by ultraviolet radiation. Some other exposures have been associated with the type of DNA damage caused by ultraviolet radiation. Therefore, people with xeroderma pigmentosum should also avoid exposure to tobacco and certain other drugs.

Prognosis

Life expectancy is significantly reduced due to morbidity associated with the cancers. Researchers have not determined how effective preventative measures are, e.g. avoidance of ultraviolet radiation.

In the 1990s scientists discovered a great deal about DNA repair mechanisms, and about the genes associated with xeroderma pigmentosum. The range of symptoms associated with each type have been better defined. The media has also been interested in XP, giving it more attention than is typical for such a rare condition. Advocates in the XP community have developed helpful resources for other affected families, such as Camp Sundown. Hopefully the first decade of 2000 will also lead to new insights, services, and possibly new treatments.

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National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse. One AMS Circle, Bethesda, MD 20892-3675. (301) 495-4484.

National Cancer Institute. Office of Communications, 31 Center Dr. MSC 2580, Bldg. 1 Room 10A16, Bethesda, MD 20892-2580. (800) 422-6237. <http://www.nci.nih.gov>.

Skin Cancer Foundation. 245 Fifth Ave., Suite 1403, New York, NY 10016. (800) 754-6490. info@skincancer.org.

Task Force on Xeroderma Pigmentosum, American Academy of Dermatology. Box 4014, Schaumburg, IL 60168-4014. (708) 330-0230.

Xeroderma Pigmentosum Registry. New Jersey Medical School, Dept. of Pathology, 185 South Orange Ave., Room C-520, Newark, NJ 07103-2714. (201) 982-4405.

Xeroderma Pigmentosum Society, Inc. PO Box 4759, Poughkeepsie, NY 12602. (518) 851-2612. xps@xps.org. <http://www.xps.org>.

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Michelle Queneau Bosworth, MS, CGC

X-linked hydrocephaly

Definition

Hydrocephaly refers to the accumulation of cerebrospinal fluid (CSF) in the fluid-filled cavities, called ventricles, that are located deep in the core of the brain. The designation *X-linked* indicates that this form of hydrocephaly results from a mutation in a **gene** that is located on the X chromosome, in this case the L1 cell adhesion molecule (L1CAM) gene.

Description

Cell adhesion molecules (CAMs) provide the traffic signals that guide the cells of developing organs to

KEY TERMS

Adducted thumbs—Thumbs clasped across the palm.

Aphasia—Loss of previously acquired ability to speak, or to understand written or spoken language.

Brain ventricles—A set of four connected cavities that are located deep in the core of the brain. Cerebrospinal fluid is made by cells lining the walls of the first two ventricles, then flows through the third, then fourth ventricle before flowing out of the brain. The fluid-filled cavities provide mechanical cushion for the brain, and the CSF provides nutrients to, and carries metabolic wastes away from, the cells of the brain.

Cell adhesion molecule—Any one of several thousand proteins that together control the cell-to-cell communication that must take place in order for cells to migrate to their proper places, develop into the proper types of cells, and make the appropriate connections with other cells.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Corticospinal tract—A bundle of long nerve fibers that runs from the motor control region of the cerebral cortex to the spinal cord, where it connects to nerves that control movement in the legs.

Cydrocephaly—Excessive accumulation of cerebrospinal fluid in the brain ventricles.

Macrocephaly—A head that is larger than normal.

Penetrance—The degree to which individuals possessing a particular genetic mutation express the trait that this mutation causes. One hundred percent penetrance is expected to be observed in truly dominant traits.

Spastic paraplegia—Inability to walk, due to lack of proper neural control over the leg muscles.

Stenosis—The constricting or narrowing of an opening or passageway.

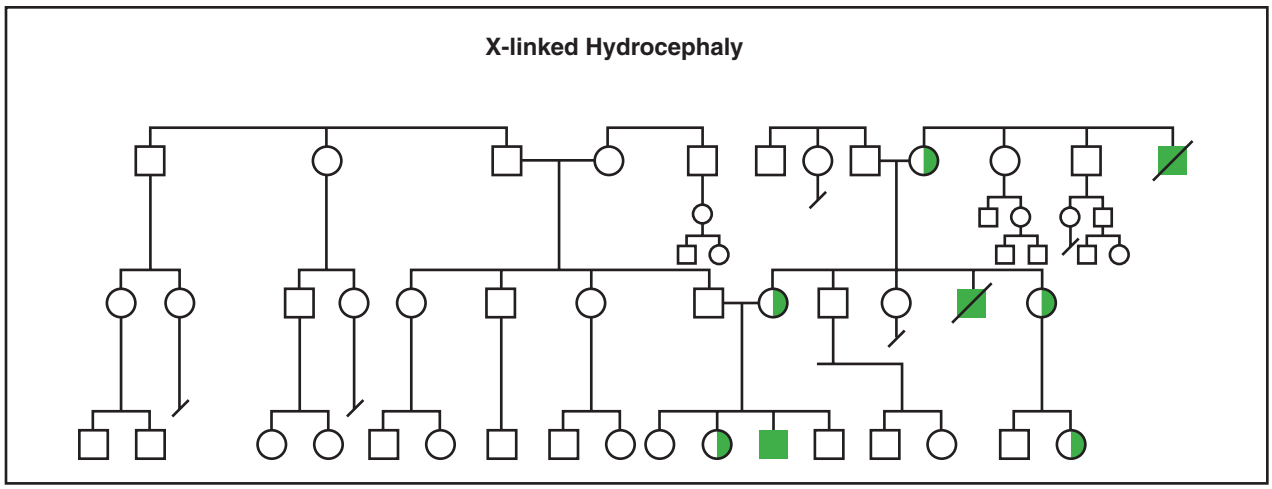
Ventriculoperitoneal shunt—A tube equipped with a low pressure valve, one end of which is inserted into the lateral ventricles, the other end of which is routed into the peritoneum, or abdominal cavity.

X-linked—Located on the X chromosome, one of the sex chromosomes. X-linked genes follow a characteristic pattern of inheritance from one generation to the next.

migrate to their proper places and make the appropriate connections with the cells with which they interact. The L1CAM protein is embedded in the membrane of nerve cell axons. Axons are projections from the nerve cell body that carry impulses to sometimes distant targets. As a developing axon grows toward its target, its leading end is capped by a growth cone similar in function to that of a plant root. The growth cone of a developing axon is rich in L1CAM. The L1CAM protein has a large, complex extracellular domain (portion of the protein outside the nerve cell), a transmembrane domain within the nerve cell membrane, and a small intracellular domain (portion inside the nerve cell). The extracellular domain acts as a feeler, and binds to CAMs that are either on the surface of other cells or floating in the extracellular fluid. The binding of the L1CAM protein to various CAMs in its environment sends signals into the nerve cell that direct the projecting axon to grow to the appropriate length, follow the course required for it to reach its target, and stop when appropriate.

The L1CAM protein is critical for proper development of several long fiber tracts in the forebrain. These include the corpus callosum, which is a thick fiber bridge that connects the left and right cerebral hemispheres, and the corticospinal tract, which extends from the motor control region of the cerebral cortex down to the spinal cord.

The developing axon often extends many cell diameters away from the cell body, and must interact with CAMs from many different sources to insure that it follows the correct route to its target. The complex extracellular domain of the L1CAM protein interacts with a variety of CAMs in the environment to serve several important functions. Because of the many functions L1CAM serves, the specific brain changes and functional handicaps that are seen in any individual patient with an L1CAM mutation depend on which of L1CAM's functions are lost and which are spared by the specific mutation that occurs in the L1CAM gene. Most families have their own unique L1CAM mutation. Some mutations abolish all of L1CAM's functions, while others change only a small



(Gale Group)

piece of the L1CAM protein. Therefore, there is marked variability between patients in terms of which brain structures are most affected and what the primary physical and behavioral symptoms will be. Because of this variability, patients with different L1CAM mutations have been given diagnoses such as X-linked hydrocephaly (XLH), X-linked spastic paraplegia type 1 (SPG1), hydrocephaly with stenosis of the aqueduct of Sylvius (HSAS), X-linked agenesis of the corpus callosum (XLACC), and MASA syndrome (mental retardation, aphasia, shuffling gait, adducted thumbs). Because these patients all presented with such different combinations of brain changes and functional handicaps, it was originally thought that these were all distinct disorders, with different biological causes. As of 2001, an effort is being made to unite these disorders under the general heading *L1CAM spectrum*, to reflect the fact that these are not distinct disorders, but merely alternative possible consequences of L1CAM mutations.

Genetic profile

The L1CAM gene is located close to the end of the long arm of the X chromosome, in the band referred to as Xq28. Since the L1CAM gene is on the X chromosome, usually only males are affected. This is because females have two X **chromosomes**, while males have only one. In a female, if one X chromosome has an L1CAM mutation on it, the non-mutated L1CAM gene on the other X chromosome can usually provide enough good L1CAM protein to support normal brain development. Males, on the other hand, having only one X chromosome, cannot compensate for an X-linked **gene mutation**.

The **inheritance** pattern for L1CAM spectrum disorders follows the typical X-linked inheritance pattern. Males are usually the only ones affected, and most females who carry L1CAM mutations are unaffected. There may be several affected brothers in a single family. In addition, in a family where the L1CAM mutation has been passed through several generations, the normally developed mothers of affected males may have affected brothers, or the normally developed sisters of affected males may have affected sons. If a female carries a mutation in L1CAM, she has a 50% chance of passing the mutation to each of her children. Therefore, approximately half her sons will be affected, and approximately half her daughters will be carriers. There is no known case in which an affected male has reproduced.

L1CAM mutations exhibit 100% penetrance, meaning that any male who has the L1CAM mutation will be affected, albeit with varying degrees of severity. This contrasts with some other disorders, in which some family members are unaffected, despite having the same gene mutation that has been seen in other affected family members.

Demographics

The incidence of hydrocephaly from all causes is approximately 1 in 2,000 live births in the general population. The X-linked form is thought to account for approximately 5% of the total cases of hydrocephaly, or approximately 1 in 25,000 to 50,000 males. In very rare cases a female may be affected, usually mildly. There are no systematic data comparing the incidence of L1CAM spectrum disorders in different races.

Signs and symptoms

Most patients with mutations in L1CAM exhibit mental retardation (MR), the degree of which can vary

from mild to severe. The vast majority also exhibit hydrocephaly, which can be mild and not require any medical intervention, or severe enough to be life-threatening. The most severe cases of hydrocephaly are associated with stenosis (narrowing or pinching closed) of the aqueduct of Sylvius. The aqueduct of Sylvius (also called the cerebral aqueduct) is a narrow channel connecting the third ventricle, located deep in the midbrain, to the fourth ventricle, located underneath the cerebellum in the posterior part of the brain. The brain's cerebrospinal fluid (CSF) is made by cells lining the first two ventricles, called the lateral ventricles, which are located in the forebrain. The CSF normally flows from the first two ventricles, through the third ventricle, then into the fourth ventricle, before flowing out of the brain. Stenosis of the aqueduct of Sylvius stops the outflow of CSF, and causes an accumulation of fluid, and pressure, primarily in the first two ventricles. Since there is no mechanism to stop CSF production in the lateral ventricles, this form of hydrocephaly is progressive. The pressure can become so great that it stretches the developing skull bones, which are still not fully hardened, resulting in the child having a head that is visibly enlarged (macrocephaly). In the process, the brain tissue is pressed against the skull, with predictably devastating effects on brain function. Many of the more severely hydrocephalic patients are either stillborn or die within one year of birth.

Approximately 80% of patients with L1CAM mutations exhibit adducted thumbs (clasped across the palm). A smaller percentage exhibit aphasia (lack of speech), or problems with leg control that range from walking with a shuffling gait to spastic paraplegia that leaves them unable to walk at all.

The most common finding in brain imaging studies is the absence (agenesis) or underdevelopment (hypoplasia) of the corpus callosum. The corpus callosum is a large fiber tract that projects between the left and right hemispheres of the brain and enables information to be transferred from one hemisphere to the other. It is uncertain whether the abnormalities in the corpus callosum are an important cause of these patients' MR. It is most likely that the pressure exerted on the developing brain tissue by the hydrocephaly is a more consistent and important cause of the MR seen in these patients. Another brain structure seen to be underdeveloped in some patients with L1CAM mutations is the corticospinal tract. The corticospinal tract begins in the motor control region of the cerebral cortex and runs downward to connect with the spinal cord neurons that control the legs. Abnormal development of the corticospinal tract is probably the cause of the shuffling gait/spastic paraplegia seen in some patients with L1CAM mutations.

Diagnosis

In the more severely hydrocephalic patients, hydrocephaly can be seen by ultrasound at 20 weeks gestation, or approximately half-way through the fetal period. For less severely affected patients, some degree of hydrocephaly is usually noted within a year after birth, along with a general developmental delay. These babies do not roll over, sit up, or reach for objects as early as babies typically do. In rarer cases, some mildly affected patients are not diagnosed until an age at which speech problems or problems with their walking gait can be observed. Adducted thumbs, when present, are noticeable from birth or are sometimes even visible upon ultrasound analysis.

Genetic testing involves a search for mutations in the L1CAM gene in patients with L1CAM spectrum disorders. The sequence of the L1CAM gene from the affected patient is compared to the normal L1CAM sequence. **DNA** is usually obtained from a blood sample for postnatal diagnosis. For prenatal diagnosis, DNA can be extracted from amniotic fluid cells obtained by **amniocentesis**, or from chorionic villus sampling.

Treatment and management

In the most severely hydrocephalic cases, the baby must be delivered by Cesarian section, because the head has grown too large by the end of the pregnancy for the baby to be delivered through the vagina. For the more severely affected patients, a ventriculoperitoneal shunt can be used to reduce the pressure inside the brain. The shunt is a tube inserted into the lateral ventricles that allows the CSF to drain into the peritoneum, or abdominal cavity. This provides a means for the CSF to flow out of the brain in cases of HSAS, in which the aqueduct of Sylvius has been closed and the CSF can not flow out of the brain by the usual channel. Shunting markedly reduces the pressure on the brain, and has saved many patients' lives. However, shunting will not prevent these patients from having MR or other L1CAM spectrum features.

Other methods for managing cases of L1CAM spectrum disorders are focused on the specific features the individual patient exhibits. Special education is almost always necessary, with the specific program designed to accommodate the degree of cognitive disability seen in the individual patient. Physical therapy and mechanical aids such as walkers can be used to help patients with milder degrees of spastic paraplegia. Speech therapy has also benefited some of the less severely aphasic patients. There is generally little improvement when these therapies are applied to more severely affected patients.

Prognosis

The prognosis for patients with L1CAM mutations is highly variable. The most severe cases of L1CAM mutations involve fetal demise, presumably because of the pressure exerted on the developing brain by the hydrocephaly. However, in less severe cases, the lifespan is determined primarily by general health and care factors. A number of patients with less severe L1CAM spectrum disorders have lived at least into their 50s.

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ORGANIZATIONS

Guardians of Hydrocephalus Research Foundation. 2618 Avenue Z, Brooklyn, NY 11235-2023. (718) 743-4473 or (800) 458-865. Fax: (718) 743-1171. guardians1@juno.com.

Hydrocephalus Association. 870 Market St. Suite 705, San Francisco, CA 94102. (415) 732-7040 or (888) 598-3789. Fax: (415) 732-7044. hydroassoc@aol.com. <http://neurosurgery.mgh.harvard.edu/ha>.

Hydrocephalus Support Group, Inc. PO Box 4236, Chesterfield, MO 63006-4236. (314) 532-8228. hydrobuff@postnet.com.

National Hydrocephalus Foundation. 12413 Centralia, Lakewood, CA 90715-1623. (562) 402-3523 or (888) 260-1789. hydrobrat@earthlink.net. <http://www.nhfonline.org>.

National Institute of Neurological Disorders and Stroke. 31 Center Drive, MSC 2540, Bldg. 31, Room 8806, Bethesda, MD 20814. (301) 496-5751 or (800) 352-9424. <http://www.ninds.nih.gov>.

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

WEBSITES

L1 Mutation Web Page. <http://dnalab-www.uia.ac.be/dnalab/l1/>.

Ron C. Michaelis, PhD, FACMG

XO syndrome *see* **Turner syndrome**

XX male syndrome

Definition

XX male syndrome occurs when the affected individual appears as a normal male, but has female **chromosomes**. Two types of XX male syndrome can occur: those with detectable SRY **gene** and those without detectable SRY **(Sex determining region Y)**. SRY is the main genetic switch for determining that a developing embryo will become male.

Description

XX male syndrome is a condition in which the sex chromosomes of an individual do not agree with the physical sex of the affected person. Normally there are 46 chromosomes, or 23 pairs of chromosomes, in each cell. The first 22 pairs are the same in men and women. The last pair, the sex chromosomes, is two X chromosomes in females (XX) and an X and a Y chromosome in males (XY).

In XX male syndrome, the person has female chromosomes but male physical features. The majority of persons with XX male syndrome have the Y chromosome gene SRY attached to one of their X chromosomes. The rest of the individuals with XX male syndrome do not have SRY detectable in their cells. Hence, other genes on other chromosomes in the pathway for determining sex must be responsible for their male physical features.

Genetic profile

In XX male syndrome caused by the gene SRY, a translocation between the X chromosome and Y chromosome causes the condition. A translocation occurs when part of one chromosome breaks off and switches places with part of another chromosome. In XX male syndrome, the tip of the Y chromosome that includes SRY is translocated to the X chromosome. As a result, an embryo with XX chromosomes with a translocated SRY gene will develop the physical characteristics of a male. Typically, a piece of the Y chromosome in the pseudoautosomal region exchanges with the tip of the X chromosome. In XX male syndrome, this crossover includes the SRY portion of the Y.

In individuals with XX male syndrome who do not have an SRY gene detectable in their cells, the cause of the condition is not known. Scientists believe that one or more genes that are involved in the development of the sex of an embryo are mutated or altered and cause physical male characteristics in a chromosomally female per-

son. These genes could be located on the X chromosome or on one of the 22 pairs of autosomes that males and females have in common. As of 2001, no genes have been found to explain the female to male sex reversal in people affected with XX male syndrome who are SRY negative. Approximately 20% of XX males do not have a known cause and are SRY negative. It is thought that SRY is a switch point, and the protein that is made by SRY regulates the activity of one or more genes (likely on an autosomal chromosome) that contribute to sex development. Also there have been some studies that demonstrate autosomal recessive and autosomal dominant **inheritance** for the XX male.

Demographics

XX male syndrome occurs in approximately one in 20,000 to one in 25,000 individuals. The vast majority, about 90%, has SRY detectable in their cells. The remaining 10% are SRY negative, although some research indicates that up to 20% can be SRY negative. XX male syndrome can occur in any ethnic background and usually occurs as a sporadic event, not inherited from the person's mother of father. However, some exceptions of more than one affected family member have been reported.

Signs and symptoms

SRY positive XX male syndrome

Males with SRY positive XX male syndrome look like and identify as males. They have normal male physical features including normal male body, genitals, and testicles. All males with XX male syndrome are infertile (cannot have biological children) because they lack the other genes on the Y chromosome involved in making sperm. Men with XX male syndrome are usually shorter than an average male, again because they do not have certain genes on the Y chromosome involved in height. A similar syndrome that effects males with two X chromosomes is **Klinefelter syndrome**. Those individuals with 46XX present with a condition similar to Klinefelter, such as small testes and abnormally long legs.

SRY negative XX male syndrome

People with SRY negative XX male syndrome are more likely to be born with physical features that suggest a condition. Many have hypospadias, where the opening of the penis is not at the tip, but further down on the shaft. They may also have undescended testicles, where the testicles remain in the body and do not drop into the scrotal sac. Occasionally, an SRY negative affected male has some female structures such as the uterus and fallopian tubes. Men with SRY negative XX male syndrome can also have gynecomastia, or breast development during puberty, and puberty can be delayed. As with SRY positive XX male syndrome, these men are infertile and shorter than average because they lack other Y specific genes. The physical features can vary within a family, but most affected people are raised as males.

A small portion of people with SRY negative XX male syndrome are true hermaphrodites. This means they have both testicular and ovarian tissue in their gonads. They are usually born with ambiguous genitalia, where the genitals of the baby have both male and female characteristics. Individuals with XX male syndrome and true hermaphrodites can occur in the same family, suggesting there is a common genetic cause to both. Research indicates that 15% of 46XX true hermaphrodites have the SRY gene.

KEY TERMS

Autosomes—Chromosome not involved in specifying sex.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Diagnosis

For people with XX male syndrome who have ambiguous genitalia, hypospadias, and/or undescended testicles, the diagnosis is suspected at birth. For males with XX male syndrome and normal male features, the diagnosis can be suspected during puberty when breast development occurs. Many men do not know they have

TABLE 1

Disorders associated with multiple X or Y chromosome inheritance

Disorder	Chromosome affected	Karotype	Incidence	Symptoms
Turner syndrome	X	45,X (monosomy)	1 in 2,000	Growth retardation Infertility Cardiovascular malformations Learning disabilities
Klinefelter syndrome	X	47,XXY (trisomy)	1 in 500–800	Taller than average Poor upper body strength; clumsiness Mild intentional tremor (20–50%) Breast enlargement (33%) Decreased testosterone production Infertility Dyslexia (50%)
Triple X	X	47,XXX (trisomy)	1 in 1,000	Mild delays in motor, linguistic and emotional development Learning disabilities Slightly taller than average
XYY syndrome	Y	47,XYY	1 in 1,000	Taller than average Lack of coordination Acne Some infertility Learning disabilities (50%) Behavior problems, especially impulse control
XX male syndrome	Y	46,X,t(X,Y) (translocation of the SRY gene [90%] or other gene responsible for male sex determination)	1 in 20,000–25,000	Usually normal male physical features but may have ambiguous genitalia, hypospadias or undescended testes Infertility Shorter than average

XX male syndrome until they try to have their own children, are unable to do so, and therefore are evaluated for infertility.

When the condition is suspected in a male, chromosome studies can be done on a small sample of tissue such as blood or skin. The results show normal sex chromosomes, or XX chromosomes. Further **genetic testing** is available and needed to determine if the SRY gene is present.

Some affected individuals have had SRY found in testicular tissue, but not in their blood cells. This is called mosaicism. Most males have only their blood cells tested for SRY and not their testicular tissue. Hence, some men who think they have SRY negative XX male syndrome may actually be mosaic and have SRY in their gonads.

XX male syndrome can be detected before a baby is born. This occurs when a mother-to-be has prenatal testing done that shows female chromosomes but on ultrasound male genitals are found. Often the mother has had prenatal testing for a reason other than XX male syndrome, such as for an increased risk of having a baby with **Down syndrome** due to her age. Genetic testing for the presence of the SRY gene can be done by an **amniocentesis**. An amniocentesis is a procedure in which a needle is inserted through the mother's abdomen into the sac of fluid surrounding the baby. Some of the fluid is removed and used to test for the presence of the SRY gene. Amniocentesis slightly increases the risk of miscarriage.

Treatment and management

For those with XX male syndrome with normal male genitals and testicles, no treatment is necessary. Affected males with hypospadias or undescended testicles may require one or more surgeries to correct the condition. If gynecomastia is severe enough, breast reduction surgery is possible. The rare person with true hermaphrodism usually requires surgery to remove the gonads, as they can become cancerous.

Parents who learn their child has been diagnosed with XX male syndrome are encouraged to gain both emotional and educational support. Issues such as explaining the condition to their child when they are grown is a topic that can be worked through with the help

of both medical professionals, and those whose own children live with the condition.

Prognosis

The prognosis for males with XX male syndrome is excellent. Surgery can usually correct any physical problems. Men with XX male syndrome have normal intelligence and a normal life span. However, all affected men will be infertile.

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ORGANIZATIONS

Intersex Society of North America. PO Box 301, Petaluma, CA 94953-0301. <http://www.isna.org>.

RESOLVE, The National Infertility Association. 1310 Broadway, Somerville, MA 02144-1779. (617) 623-0744. resolveinc@aol.com.

Carin Lea Beltz, MS, CGC

XYY syndrome

Definition

XYY syndrome is a chromosome disorder that affects males. Males with this disorder have an extra Y chromosome.

Description

The XYY syndrome was previously considered the *super-male* syndrome, in which men with this condition were thought to be overly aggressive and more likely to become criminals. These original stereotypes came about because several researchers in the 1960s found a high number of men with XYY syndrome in prisons and mental institutes. Based on these observations, men with XYY syndrome were labeled as overly aggressive and likely to be criminals.

These original observations did not consider that the majority of males with XYY syndrome were not in prisons or mental institutes. Since then, broader, less biased studies have been done on males with XYY syndrome. Though males with XYY syndrome may be taller than average and have an increased risk for learning difficulties, especially in reading and speech, they are not overly aggressive. Unfortunately, some text books and many people still believe the inaccurate stereotype of the *super-male* syndrome.

Genetic profile

Chromosomes are structures in the cells that contain genes. Genes are responsible for instructing our bodies how to grow and develop. Usually, an individual has 46 chromosomes in his or her cells, or 23 pairs. The first 22 pairs are the same in males and females and the last pair, the sex chromosomes, consist of two X chromosomes in a female, and an X chromosome and an Y chromosome in a male.

XYY syndrome occurs when an extra Y chromosome is present in the cells of an affected individual. People with XYY syndrome are always male. The error that causes the extra Y chromosome can occur in the fertilizing sperm or in the developing embryo.

XYY is not considered an inherited condition. An inherited condition usually is one in which the mother and/or father has an alteration in a **gene** or chromosome that can be passed onto their children. Typically, in an inherited condition, there is an increased chance that the condition will reoccur. The risk of the condition reoccurring in another pregnancy is not increased above the general population incidence.

Demographics

XYY syndrome has an incidence of one in 1,000 newborn males. However, since many males with XYY syndrome look like other males without XYY syndrome, many males are never identified.

Signs and symptoms

There are no physical abnormalities in most males with XYY syndrome. However, some males can have one or more of the follwing characteristics. Males who have XYY syndrome are usually normal in length at birth, but have rapid growth in childhood, typically averaging in the 75th percentile (taller than 75% of males their same

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

age). Many males with XYY syndrome are not overly muscular, particularly in the chest and shoulders. Individuals with XYY syndrome often have difficulties with their coordination. As a result, they can appear to be awkward or clumsy. During their teenage years, males with XYY syndrome may develop severe acne that may need to be treated by a dermatologist.

Men with XYY syndrome have normal, heterosexual function and most are fertile. However, numerous case reports of men with XYY syndrome presenting with infertility have been reported. Most males with XYY syndrome have normal hormones involved in their sperm production. However, a minority of males with XYY syndrome may have increased amounts of some hormones involved in sperm production. This may result in infertility due to inadequate sperm production. As of 2001, the true incidence of infertility in males with XYY syndrome is unknown.

When XYY men make sperm, the extra Y chromosome is thought to be lost resulting in a normal number of sex chromosomes. As a result, men with XYY syndrome are not at an increased risk for fathering children with chromosome abnormalities. However, some men with XYY syndrome have been found to have more sperm with extra chromosomes than what is found in men without XYY syndrome. Whether these men have an increased risk of fathering a child with a chromosome abnormality is unknown as of 2001.

Men with XYY syndrome usually have normal intelligence, but it can be slightly lower than their brothers and sisters. Approximately 50% of males with XYY syndrome have learning difficulties, usually in language and reading. Speech delay can be noticed in early school years. Males with XYY syndrome may not process information as quickly as their peers and may need additional time for learning.

Males with XYY syndrome have an increased risk of behavior problems. Hyperactivity and temper tantrums can occur more frequently than expected, especially during childhood. As males with XYY syndrome become older, they may have problems with impulse control and appear emotionally immature.

From a psychosocial standpoint, males with XYY syndrome may have low self-esteem due to mild learning disabilities and/or lack of athletic skills due to lack of coordination. Males with XYY syndrome are at risk in stressful environments and have a low ability to deal with frustration.

As of 2001, men with XYY syndrome are not thought to be excessively aggressive or psychotic. However, because some men with XYY syndrome can have mild learning difficulties and/or have difficulty controlling behavior problems such as lack of impulse control, their actions may lead to criminal behavior if placed in the right environment. It is important to emphasize that this occurs only in a small percentage of men with XYY syndrome. Most men with XYY syndrome are productive members of society with no criminal behavior.

Diagnosis

Most individuals with 47,XYY go through their entire lives without being diagnosed with this condition.

Chromosome studies can be done after birth on a skin or blood sample to confirm the condition. This syndrome can also be diagnosed coincidentally when a pregnant mother undergoes prenatal testing for other reasons, such as being age 35 or older at the time of delivery. Prenatal tests that can determine whether or not an unborn baby will be affected with 47,XXY are the chorionic villi sampling (CVS) and **amniocentesis** procedures. Both procedures are associated with potential risks of pregnancy loss and therefore are only offered to women who have an increased risk of having a baby born with a chromosome problem or some type of genetic condition.

Treatment and management

Treatment and management for most men with XYY syndrome is not indicated. However, early identification and intervention of learning disabilities and/or behavior difficulties is necessary. Speech therapy, physical therapy, and occupational therapy may be helpful for males with XYY syndrome. Also, because males with XYY syndrome are at risk in stressful environments, a supportive and stimulating home life is important.

Prognosis

Most males who have learning disabilities and/or behavior problems due to XYY syndrome have an excellent prognosis. Learning disabilities are mild and most affected males learn how to control their impulsiveness and other behavior problems. XYY syndrome does not shorten lifespan.

Resources

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ORGANIZATIONS

Chromosome Deletion Outreach, Inc. PO Box 724, Boca Raton, FL 33429-0724. (561) 391-5098 or (888) 236-6880. Fax: (561) 395-4252. cdo@worldnet.att.net. <http://members.aol.com/cdousa/cdo.htm>.

Carin Lea Beltz, MS, CGC

Z

Zellweger syndrome

Definition

Zellweger syndrome refers to an inherited condition that is present at birth and usually causes death during the first six to twelve months of age. This syndrome is caused by a lack or reduction of peroxisomes, which are specialized organelles that help the body get rid of toxic substances. Zellweger syndrome is a disorder of metabolism. It is one of a group of **genetic disorders** called the leukodystrophies, diseases that involve abnormal growth of the fatty covering of nerve fibers (myelin sheath).

Description

In 1964, reserchers described a similar pattern of multiple birth defects in two unrelated pairs of siblings in Iowa and Maryland. Hans Zellweger identified the cases in Iowa. Passarge and McAdams reported several similar cases and introduced the name cerebro-hepato-renal-syndrome. Opitz reviewed the Bowen report and decided that only the Iowa cases represented the same condition reported by others. To recognize Hans Zellweger's role in identifying the Iowa cases, Opitz proposed the name Zellweger cerebro-hepato-renal syndrome. Most refer to the syndrome as Zellweger syndrome.

Initially, Zellweger syndrome was considered a multiple congenital anomaly disorder. In 1973, researchers reported that individuals who have Zellweger syndrome do not have peroxisomes in their liver and kidneys. Important metabolic processes take place in peroxisomes. Thus, the first evidence that Zellweger syndrome should be reassigned to the metabolic disease category was provided.

Metabolism includes numerous chemical processes involved in both construction (anabolism) and break down (catabolism) of important components. These processes are catalyzed (or helped along) by enzymes. If any enzymes are missing in the process, a build-up of an initial substance, or a missing end-product, can result. Either of these situations can lead to disease.

Peroxisomes are small organelles found in cells, particularly of the liver, kidneys, and brain. Substances that are broken down in peroxisomes include very long chain fatty acids, polyunsaturated fatty acids, dicarboxylic fatty acids, prostaglandins, and the side chain of cholesterol. When peroxisomes are absent or deficient, very long chain fatty acids, and other substances that peroxisomes normally help to catalyze, begin to build up in the body.

Peroxisomes also play a part in the initial reactions in the creation of plasmalogens. Plasmalogens are important components in the structure of myelin, a fatty layer that covers the nerve fibers in the body. This covering helps the nerve signals to move correctly from place to place. Since plasmalogens require peroxisomes for their formation, a lack of functioning peroxisomes causes a

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

deficiency in plasmalogens. Since the plasmalogens are required for the formation of myelin, the myelin is defective.

Bile acid formation also requires peroxisomes. Bile is secreted by the liver and stored in the gallbladder. It is released when fat enters the intestines. Bile then helps to break down these fats to prepare them for further digestion. Bile acid is produced during the breakdown of cholesterol.

Babies with Zellweger syndrome have severe developmental retardation and impairment of their central nervous system. They lack muscle tone (hypotonia), and are often blind or deaf. They have a distinctive facial appearance, an enlarged liver, and may have cysts in their kidneys. They will frequently have jaundice in the newborn period that is more serious and lasts longer than usual. Jaundice is a yellow discoloration of the skin and eyes caused by too much bilirubin in the blood. It may be a symptom of many disorders including liver disease. Healthy newborns frequently have jaundice that resolves after a few days.

Genetic profile

Zellweger syndrome is an autosomal recessive condition. This means that in order to have the condition, an individual needs to inherit one copy of the **gene** for Zellweger syndrome from each parent. An individual who has only one copy of the gene is called a carrier for the condition and does not have any signs or symptoms of the condition. When two parents are carriers for Zellweger syndrome, they have a 25% chance, with each pregnancy, for having an affected child. They have a 50% chance for having a child who is a carrier for the condition and a 25% chance for having a child who is neither affected nor a carrier for Zellweger syndrome.

Changes or mutations in any of several different genes involved in the creation of peroxisomes (peroxisome biogenesis) can cause Zellweger syndrome. There are many gene mutations that have been identified that are involved with the creation of functioning peroxisomes. The gene located on the long arm of chromosome 7, at 7q21-q22, is in part responsible for the creation of peroxisomes. The gene product is called peroxisome biogenesis factor 1 or Peroxin 1 (PEX 1). When a gene change or mutation occurs in this area that does not allow for normal creation of the peroxisomes, then the peroxisomes are not created, leading to Zellweger syndrome. There are several other genes identified on different **chromosomes** that will not allow for normal peroxisome development if a **gene mutation** occurs. These include, but are not limited to, peroxisome biogenesis factor 13 (short arm of chromosome 2 at 2p15), peroxisome biogenesis factor 6 (short arm of chromosome 6 at 6p21), peroxisome assembly factor-1 (long arm of chromosome 8 at 8q21), peroxisomal targeting signal 1 receptor (short arm of chromosome 12 at 12p13), and peroxisome biogenesis factor 10 (chromosome 1).

The cause of Zellweger syndrome is a failure of the peroxisomes to be able to bring newly created peroxisomal proteins into the peroxisomes. Instead, the proteins stay outside of the peroxisomes and are broken down. The peroxisome membranes may be present, but are empty, like the wood frame of an empty house. These empty peroxisomes have been called peroxisome "ghosts."

Demographics

The frequency of this condition is estimated to be 1 in 50,000. There is no reported difference in the incidence in any particular sex or ethnic background.

Signs and symptoms

The characteristic facial features of Zellweger syndrome include:

- high forehead
- widely spaced eyes (hypertelorism)
- low, broad, or flat nasal bridge
- "full" cheeks
- small chin (micrognathia)
- forward tilting (anteverted) nostrils
- vertical fold of skin over the inner corner of the eye (epicanthal fold)
- upslanting eyes
- shallow orbital ridges
- minor ear abnormalities

Other characteristics include, but are not limited to:

- breech presentation at birth (feet first)
- extremely weak muscles (hypotonia)
- weak sucking and swallowing reflexes
- high arched palate
- absent deep tendon reflexes
- seizures
- deafness
- enlarged liver (hepatomegaly)
- enlarged spleen

- gastrointestinal bleeding
- slow growth after birth
- severe mental retardation
- abnormal brain findings
- involuntary, rhythmic movements of the eyes (nystagmus)
- large space between the bones of the skull (fontanel)
- flat back part of the head (occiput)
- tiny white or yellow spots on the colored part of the eyes (brushfield spots)
- redundant skin on neck
- congenital cloudy lenses of the eye (cataracts)
- possible heart defects
- a single crease across the palm of the hands (simian creases)
- fixed, immovable joints (contractures)
- misaligned bones in the front part of the foot/club foot (talipes equinovarus)
- undescended testicles (cryptorchidism)
- underdeveloped thymus (thymus hypoplasia)
- hearing impairment
- failure to thrive
- psychomotor retardation
- high levels of iron or copper in the blood

Diagnosis

Diagnosis is based on clinical characteristics combined with a series of tests to determine the peroxisomal function and structure. Biochemical abnormalities include elevated levels of very long chain fatty acids, a decrease in the levels of a peroxisomal enzyme dihydroxyacetone phosphate acyltransferase (DHAPAT), the presence of abnormal intermediates in bile acid formation, and a lack of plasmalogens in a blood sample. Absence of peroxisomes in liver biopsy specimen is considered essential for the diagnosis of Zellweger syndrome.

Prenatal diagnosis for Zellweger syndrome is possible through chorionic villus sampling (CVS) and **amniocentesis**. Diagnosis may be made by measuring the synthesis of plasmalogens in cultured CVS or amniotic fluid cells or by measuring the amount of very long chain fatty acids. Other tests may be useful, including measuring the amount of the peroxisomal enzyme DHAPAT in the amniotic fluid.

There are other leukodystrophies, including neonatal adrenoleukodystrophy, **infantile Refsum disease**, and hyperpipecolic acidemia. The milder diseases may be due to having partial peroxisome function.

Treatment and management

In general there is no cure and no treatment for Zellweger syndrome.

Prognosis

The prognosis for individuals who have Zellweger syndrome is poor. Those with the disease usually only live for a few months after birth. Rarely do individuals with Zellweger syndrome live longer than one year.

Resources

BOOKS

Jones, Kenneth Lyons, ed. *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia: W.B. Saunders Company, 1997.

ORGANIZATIONS

National Organization for Rare Disorders (NORD). PO Box 8923, New Fairfield, CT 06812-8923. (203) 746-6518 or (800) 999-6673. Fax: (203) 746-6481. <http://www.rarediseases.org>.

United Leukodystrophy Foundation. 2304 Highland Dr., Sycamore, IL 60178. (815) 895-3211 or (800) 728-5483. Fax: (815) 895-2432. <http://www. ulf.org>.

WEBSITES

"NINDS Zellweger Syndrome Information Page." National Institute of Neurological Disorders and Stroke. <http://www.ninds.nih.gov/health_and_medical/disorders/zellwege_doc.htm>.

Renée A. Laux, MS

Zygote

Definition

The zygote is the single cell that is formed when the sperm cell fertilizes the egg cell. The zygote divides multiple times, producing identical copies of itself. The cells produced by the division of the zygote form the developing embryo, fetus, and baby. The zygote is the first step in the formation of a new person.

Description

When the sperm fuses with the egg, a cascade of events begins. Additional sperm are prevented from fer-

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

Teratogen—Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

tilizing the egg. The membranes of the egg and sperm combine, producing one single cell. The egg and sperm prepare to fuse their genetic material (**DNA**/chromosomes). Finally, the genetic material combines to produce the zygote with one complete set of **chromosomes**.

Most cells in the human body have two pairs of 23 chromosomes, i.e. 46 chromosomes total. One set of 23 chromosomes is inherited from the mother, and the complementary set is inherited from the father. When the egg and sperm are formed, the two sets of chromosomes divide evenly, from 46 to 23 chromsomes to produce eggs and sperm with 23 chromosomes each. This ensures that when the egg and sperm fuse during conception, the original number of chromosomes (46) is restored.

The reduction of each parent cell from 46 to 23 chromosomes ensures that each parent contributes half of his or her genetic material to form the zygote and the offspring shares 50% of his or her genes with each parent. Duplication of the single zygote occurs through a complete division of the single ball of cells. This begins the process of forming the fetus and eventually the baby. The first division produces two identical cells, the second produces four cells, the third produces eight cells, etc. After many cell divisions, the cells begin to specialize and differentiate (form particular tissues and organs).

Fertilization usually occurs in the fallopian tube, and the first few cell divisions occur as the developing embryo moves to the uterus. The first division occurs about 30 hours after fertilization. As the zygote divides, some of the cells formed will develop into the placenta. Approximately six days after fertilization, the ball of cells attaches to the uterine wall.

Sex determination

Men and women each have 22 pairs of non-sex chromosomes and two sex chromosomes. Men's sex chromosomes are X and Y. A mature sperm cell that has undergone the chromosome division process from 46 to 23 chromosomes produces a cell that is either X or Y. Women's sex chromosomes are X and X. The eggs that women produce have only X chromosomes. Therefore, the sperm determines whether the zygote is XY or XX, which is the initial step on the biological path to becoming a male or female.

Developmental periods

The term *embryo* refers to the developing baby between the second week after conception and the eighth week after conception. Doctors use the term *fetus* from the ninth week after conception to birth. A pregnancy is broken down into three trimesters. The first trimester begins with the first day of the woman's last menstrual period and each *trimester* is three calendar months.

Twins

Twins may arise in two ways. Identical twins are called "monozygotic" because both individuals are formed from the same zygote. As the zygote divides to form the baby, two separate individuals form instead of one. Fraternal twins are called "dizygotic" because each individual develops from a different zygote. Two eggs are ovulated, and a separate sperm fertilizes each egg. Therefore, identical twins have exactly the same DNA in each cell and fraternal twins share the same amount of DNA as brothers and sisters. Sometimes it is impossible to tell monozygotic twins from dizygotic twins based on the placenta and the fetal membranes. If a person wants to determine whether twins are monozygotic or dizygotic, DNA studies of blood cells will provide a definitive answer.

Abnormalities

The zygote normally contains two complete sets of 23 chromosomes, and two copies of every **gene**. If the egg or sperm that fuse to form the zygote is abnormal, the zygote will also be abnormal. For example, **Down syndrome** is caused by an extra chromosome number 21 from the egg or sperm cell. Since the cells formed by division of the zygote are identical to the zygote, any abnormality in the zygote will be in every cell of the baby.

Abnormalities can also arise when the zygote begins to divide. This type of abnormality is usually severe, eventually leading to a miscarriage. If an abnormality occurs after the zygote has divided one or more times, the baby will have some normal cells and some abnormal cells. This situation is referred to as "mosaicism" and "mosaic" may be used to describe the person's condition.

Molar pregnancies

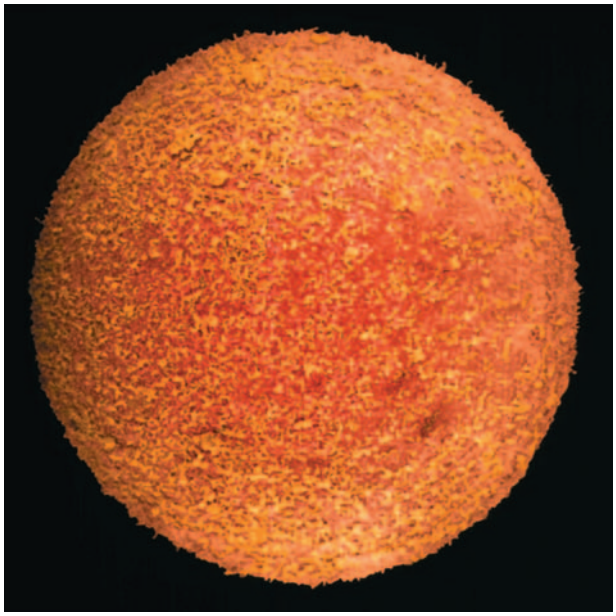
Molar pregnancies can occur in one of two ways. Sometimes the original cell that duplicates and divides to form the fetus is completely of paternal origin. The chromosomes in a sperm duplicate themselves, then proceed to divide as if they were a normal zygote. These pregnancies are completely abnormal and miscarry. Another type of molar pregnancy occurs when two sperm fertilize one egg. The zygote is triploidy and has 69 chromosomes instead of 46. Although some fetal parts can be seen, these pregnancies normally miscarry in the first or second trimester.

Birth defects

The term *birth defect* describes many different types of abnormalities, including physical malformations. Abnormalities of anatomical structures may be significant or insignificant; minor variations in structure are common. Approximately 3% of newborns have major malformations. The causes are: chromosome abnormalities (6–7%), inherited genetic conditions (7-8%), environmental factors (7–10%), and multifactorial causes (20–25%). The cause of the remaining 50–60% of malformations is unknown. *Multifactorial* refers to causes with both genetic and environmental components. Environmental factors include exposures to drugs, chemicals, or other substances that affect the development of the fetus while he/she is in the uterus. Substances that cause birth defects are referred to as teratogens.

Artificial reproductive technology

Couples may pursue assisted reproductive technologies for a number of reasons. If a couple has *artificial insemination*, the sperm is inserted into the uterus when the woman in ovulating. Fertilization then occurs as it would normally. If a couple has *in vitro fertilization* (IVF), the egg and sperm are mixed outside the body in the laboratory. The zygote forms in a petri dish if fertilization occurs. After a number of cell divisions, the developing embryo is placed in the woman's uterus. If the sperm are incapable of fusing with the egg themselves, the sperm may be injected into the egg. This additional step to the IVF procedure is called *intracytoplasmic sperm injection* (ICSI).



A human zygote. *(Photo Researchers, Inc.)*

In the year 2001, *preimplantation diagnosis* is possible for a number of genetic diseases. Couples may pursue this if they are at a significant risk for having a child with a disease that could be diagnosed prior to becoming pregnant through preimplantation diagnosis. The procedure is like that of in vitro fertilization, with an additional step. After fertilization occurs and the zygote has begun to divide, a single cell is removed. Removing the cell does not harm the other cells. The cell that is removed is tested for the genetic disease for which the couple is at risk. Multiple developing embryos are tested. Only the embryos that do not have the condition are placed in the woman's uterus to complete development.

The development of a person from the zygote is a fascinating and amazing process. It is a difficult area to study because scientists cannot manipulate human embryos to observe the effects, and the development of the fetus cannot be directly observed. Researchers still have many unanswered questions. Following a doctor's recommendations from prior to the pregnancy throughout pregnancy (such as folic acid intake and avoidance of alcohol and other drugs) increases the chances that the development of a zygote into a full-term infant will be normal. However, there are many babies born with severe birth defects or genetic diseases despite the parents' efforts at doing everything in their power to prevent a problem. Most birth defects and **genetic disorders** occur because of an event out of control of the parents.

Resources

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Agnew, Connie L. *Twins!: Expert Advice From Two Practicing Physicians on Pregnancy, Birth, and the First Year.* New York: HarperCollins, 1997.

Brasner, Shari E. *Advice From a Pregnant Obstetrician.* New York: Hyperion, 1998.

Nathanielsz, P.W. *Life in the Womb: The Origin of Health and Disease.* Ithaca, NY: Promethean Press, 1999.

Vaughn, Christopher C. *How Life Begins: The Science of Life in the Womb.* New York: Times Books, 1996.

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Check, Erika. "What Moms Can Do Now." *Newsweek* (27 September 1999): 57–58.

Christensen, Damaris. "Sobering Work." *Science News* (8 July 2000): 28–29.

Kowalski, Kathiann. "High-tech Conception in the 21st Century." *Current Health* (January 2000): 1–4.

Miller, Annetta, and Joan Raymond. "The Infertility Challenge." *Newsweek* (Spring/Summer 1999 Special Edition): 26–28.

ORGANIZATIONS

American College of Obstetricians and Gynecologists. PO Box 96920, 409 12th St. SW, Washington, DC 20090-6920. <http://www.acog.org>.

American Society for Reproductive Medicine. 1209 Montgomery Highway, Birmingham, AL 35216-2809. (205) 978-5000. asrm@asrm.org. <http://www.asrm.org>.

RESOLVE, The National Infertility Association. 1310 Broadway, Somerville, MA 02144-1779. (617) 623-0744. resolveinc@aol.com. <http://www.resolve.org>.

WEBSITES

The InterNational Council on Infertility Information Dissemination, Inc. <http://www.inciid.org>.

Maternal and Child Health Bureau. <http://www.mchb.hrsa.gov/>.

Organization of Teratology Information Services. <http://www.otispregnancy.org/index.html>.

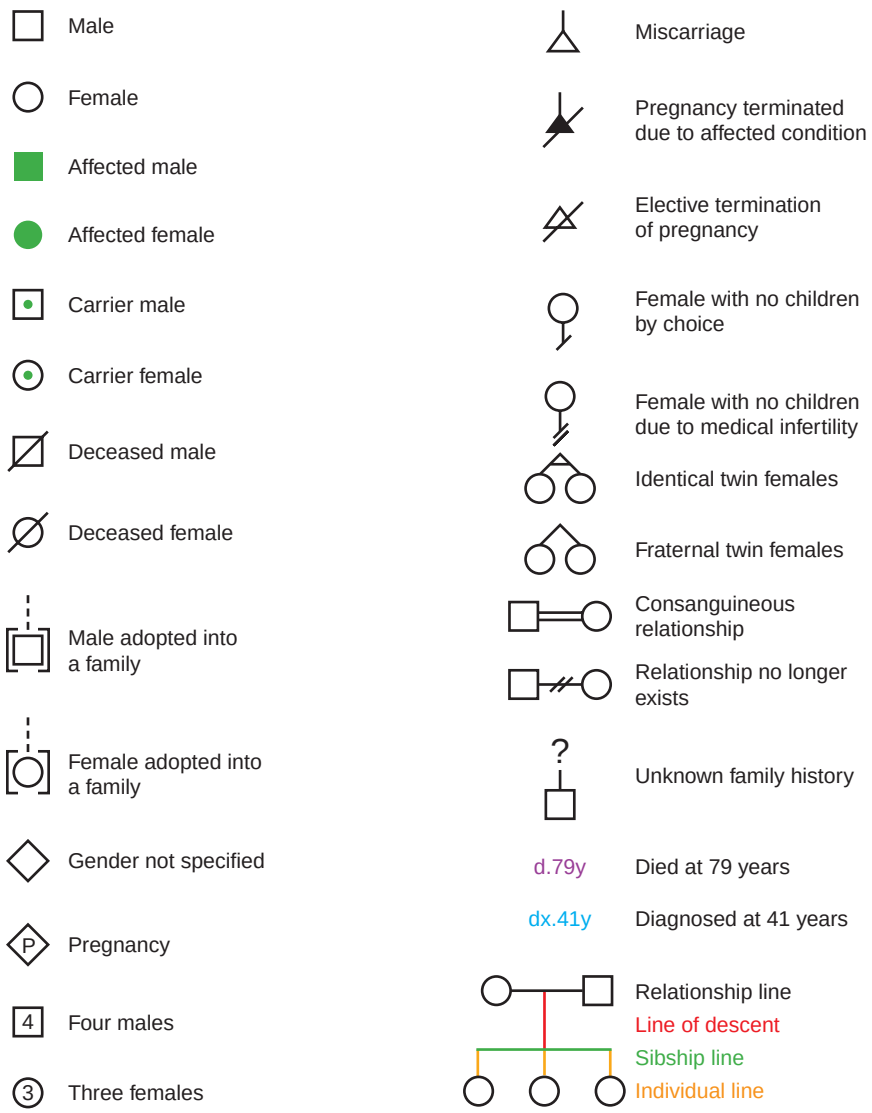
Michelle Queneau Bosworth, MS, CGC

SYMBOL GUIDE FOR PEDIGREE CHARTS

Pedigree charts are a visual tool for documenting biological relationships in families and the presence of disorders. Using these charts, a medical professional such as a geneticist or genetic counselor, can analyze the genetic risk in a family for a particular trait or condition by tracking which individuals have the disorder and determining how it is inherited.

A standard set of symbols has been established for use in creating pedigree charts. Those found within the body of several entries in the encyclopedia follow the symbol guide explained on the next page. The exact style and amount of information presented on the chart varies for each family and depends on the trait or condition under investigation. Typically, only data that is directly related to the disorder being analyzed will be included.

Symbol Guide for Pedigree Charts



CHROMOSOME MAP

A chromosome map indicates the relative positions of the genes that code for certain characteristics. The basic format for writing a gene position is the chromosome number, arm, band, sub-band, and sub-sub-band, if known. An example is 3p22.5.

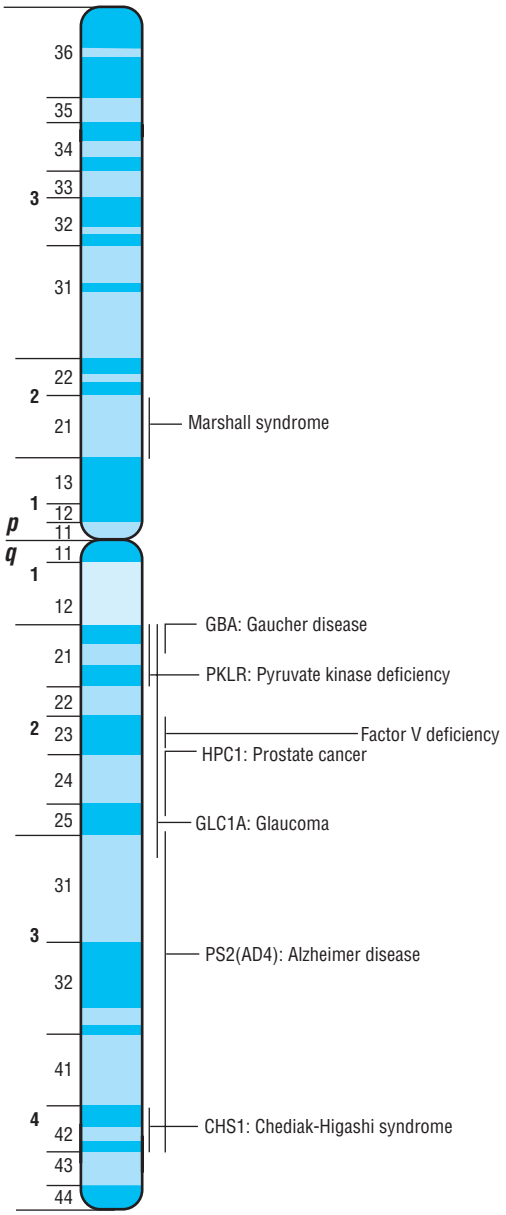
The chromosome number refers to one of the 22 autosomal chromosomes (numbered 1-22) or one of the sex-determining chromosomes known as X or Y. In the example, the gene is on chromosome 3.

Each chromosome has two arms, separated by a centromere, the pinched-in area toward the top of the chromosome. The short arm, labeled “p”, is above the centromere and the long arm, “q”, is below it. In the case of the example gene, it is found on the short arm (p) of chromosome 3, or 3p.

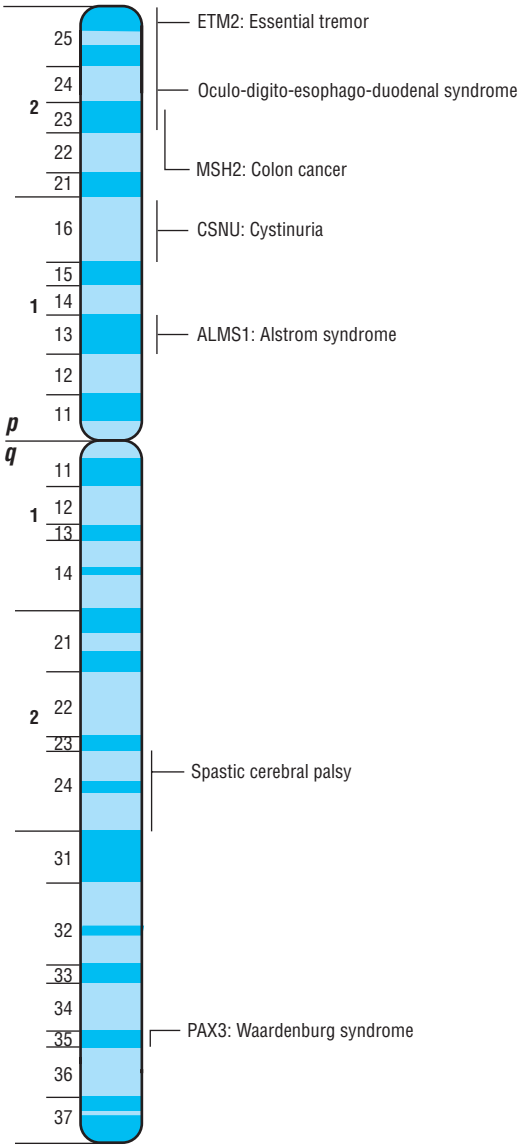
The arms are further divided into cytogenetic bands (regions) numbered 1, 2, 3, etc... The numbers start at the centromere and increase to the end of the arm, known as the telomere. These bands can only be seen when stained and viewed under a microscope. Sub-bands, which are numbered the same way as bands, may be visible within bands at greater magnifications. Therefore, the exact location of the example gene is the short arm (p) of chromosome 3, band 2, sub-band region 2, and a sub-sub band 5.

The following 24 illustrations demonstrate the approximate gene location for several of the genes relating to disorders mentioned in this encyclopedia. Disorders known to be related to a specific chromosome but not necessarily at an exact location have been placed below the chromosome. These chromosome maps are in no way complete, rather, they provide an introduction to understanding relative size differences of human chromosomes and where geneticists have located the genes associated with the source of certain genetic disorders.

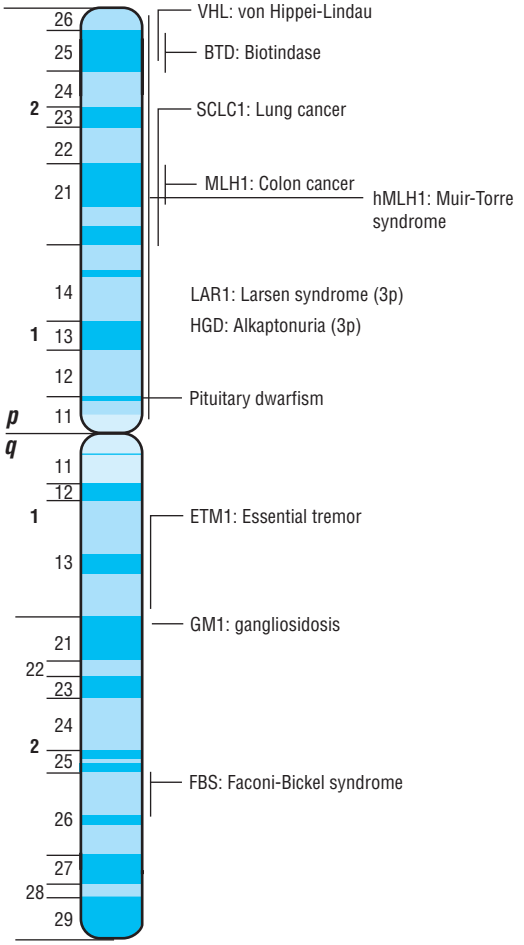
Chromosome 1



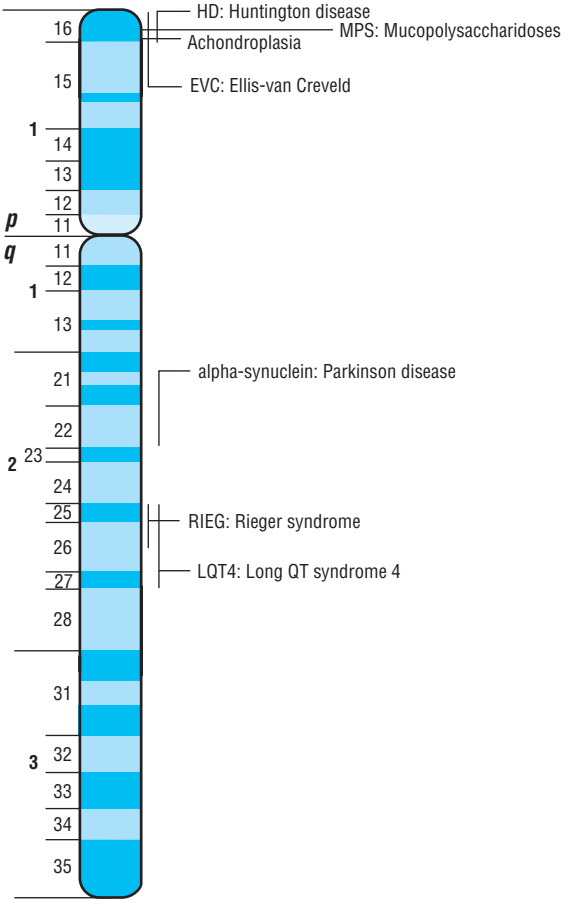
Chromosome 2

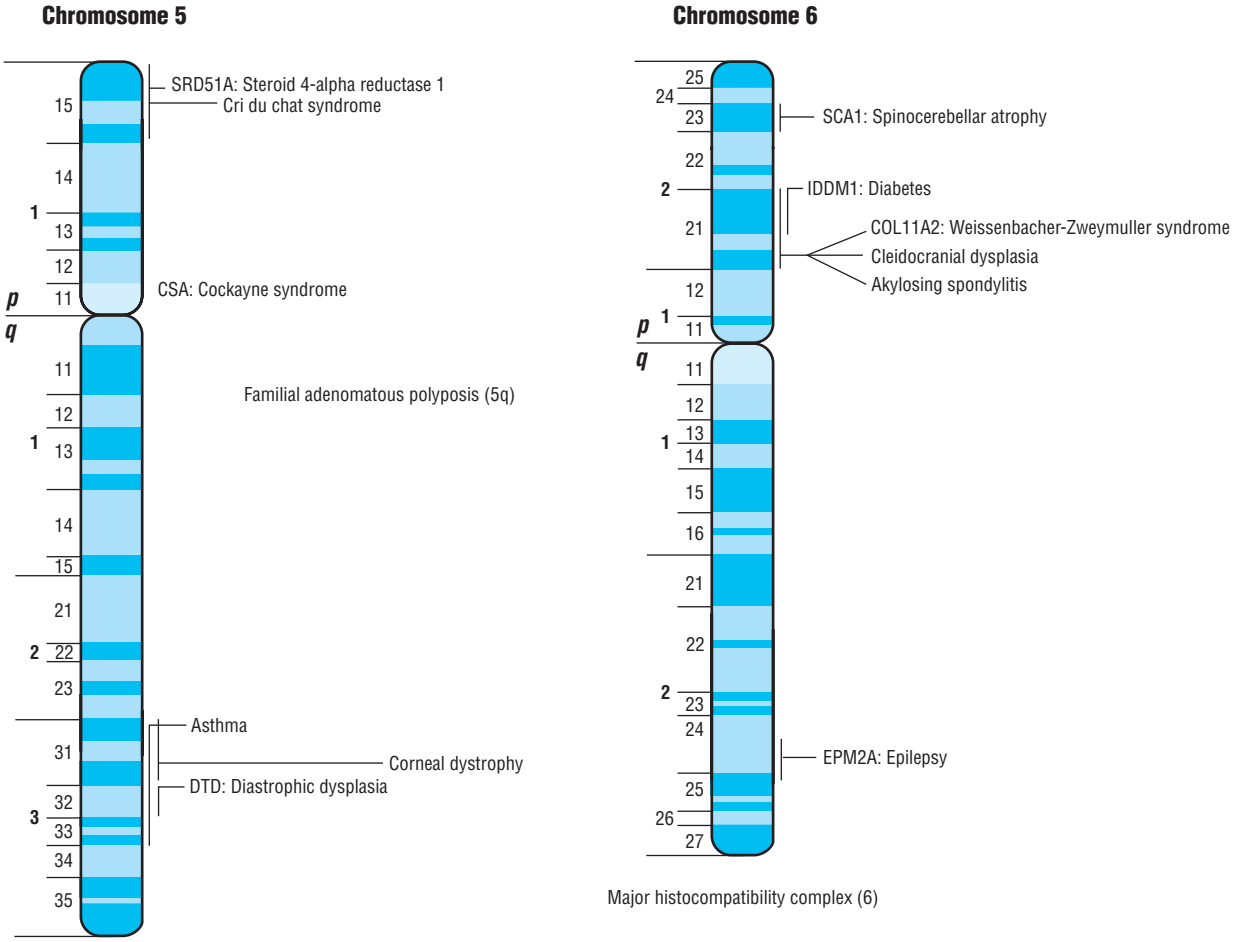


Chromosome 3

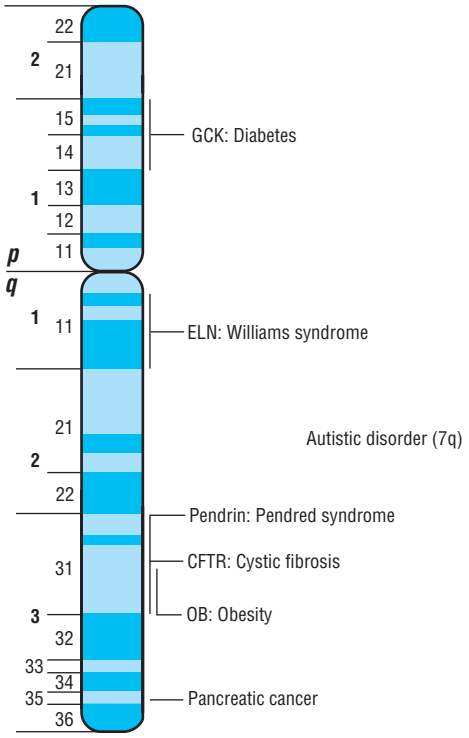


Chromosome 4

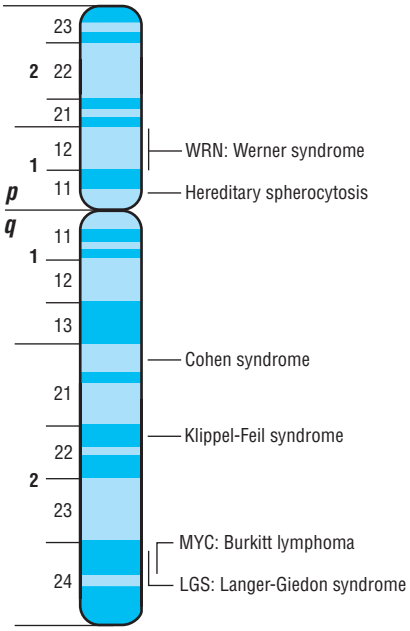



Chromosome 5
SRD51A: Steroid 4-alpha reductase 1
Cri du chat syndrome
CSA: Cockayne syndrome
Familial adenomatous polyposis (5q)
Asthma
Corneal dystrophy
DTD: Diastrophic dysplasia
Chromosome 6
SCA1: Spinocerebellar atrophy
IDDM1: Diabetes
COL11A2: Weissenbacher-Zweymuller syndrome
Cleidocranial dysplasia
Akylosing spondylitis
EPM2A: Epilepsy
Major histocompatibility complex (6)

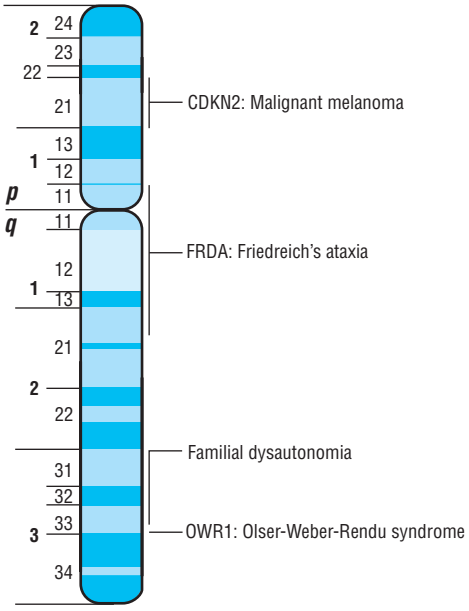
Chromosome 7



Chromosome 8

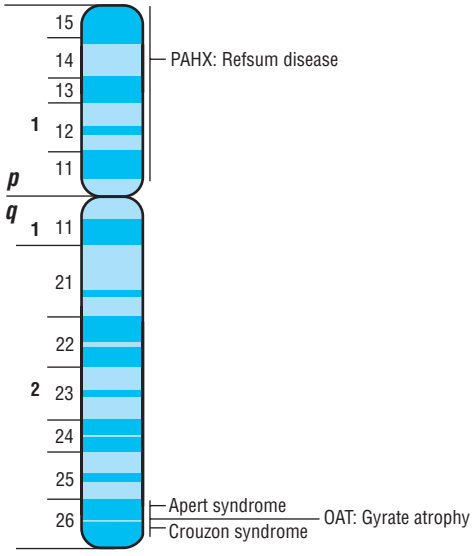


Chromosome 9

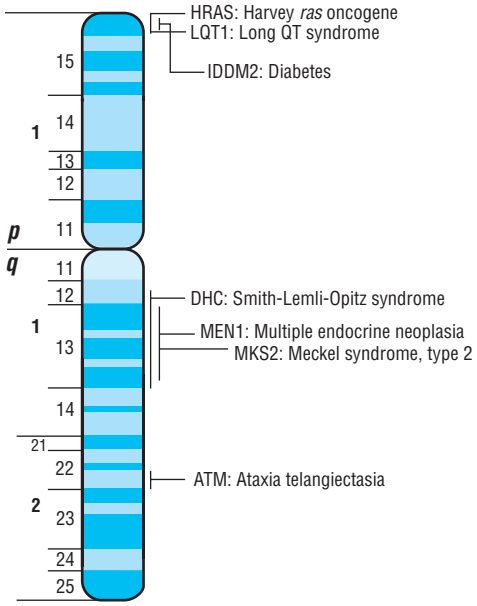


Distal arthrogryposis syndrome (9)

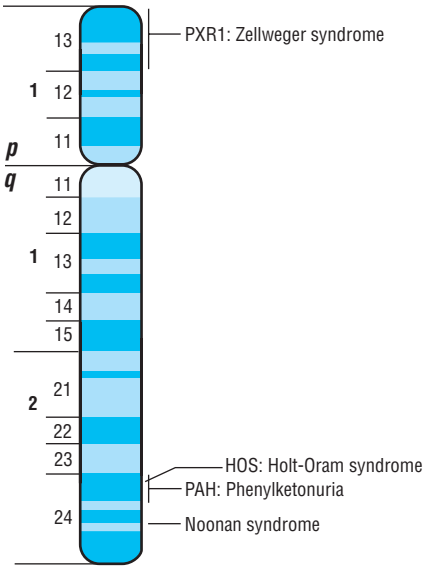
Chromosome 10



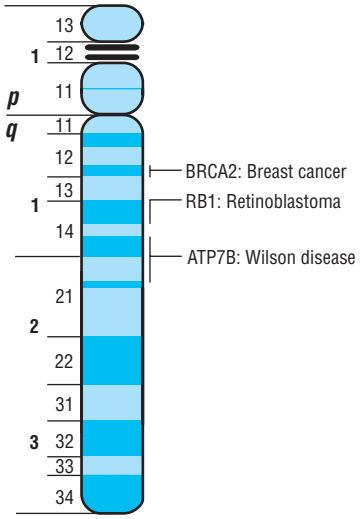
Chromosome 11



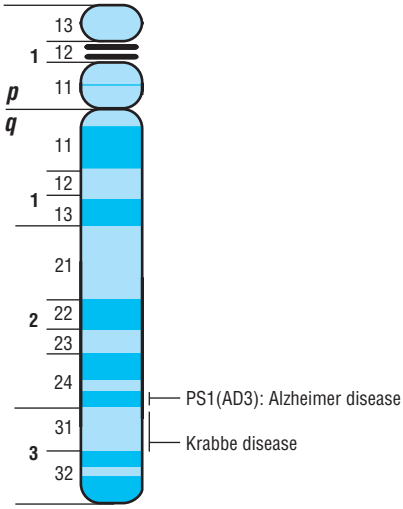
Chromosome 12



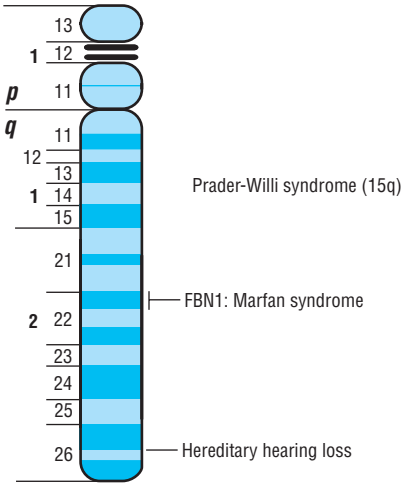
Chromosome 13



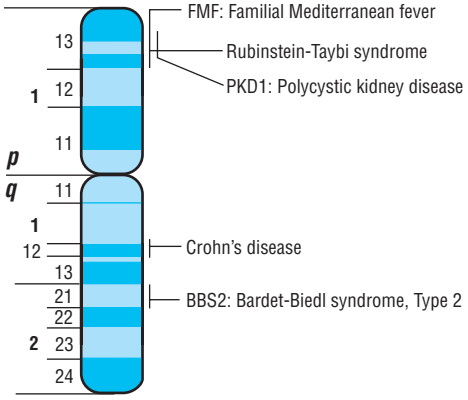
Chromosome 14



Chromosome 15

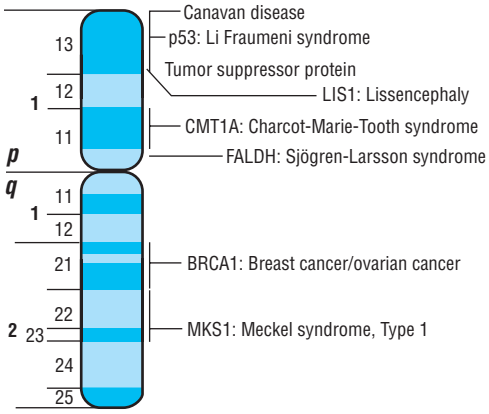


Chromosome 16



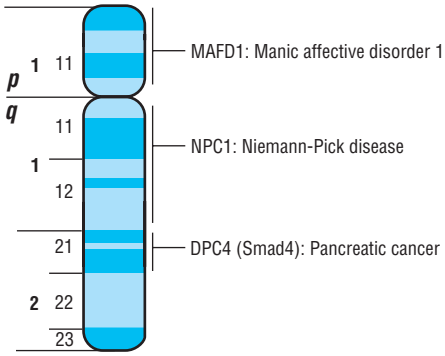
ABCC6: Pseudoaxanthoma elasticum (16)

Chromosome 17

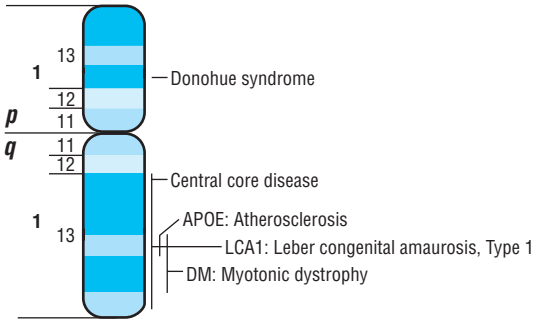


SOX9: Campomelic dysplasia

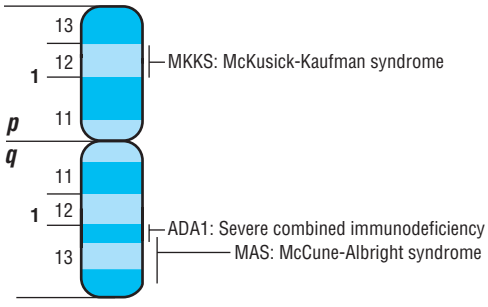
Chromosome 18



Chromosome 19

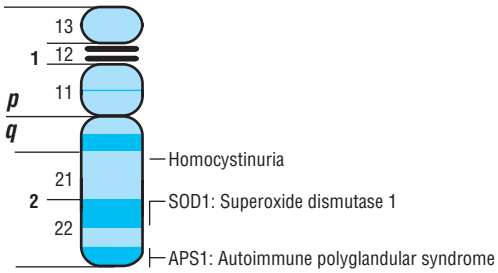


Chromosome 20

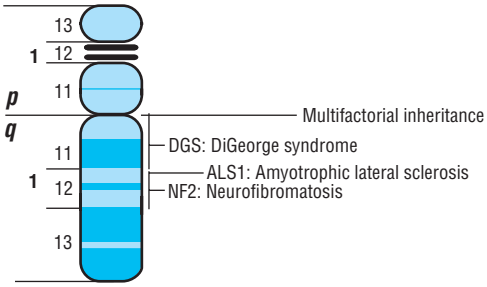


CDMP1: Brachydactyly

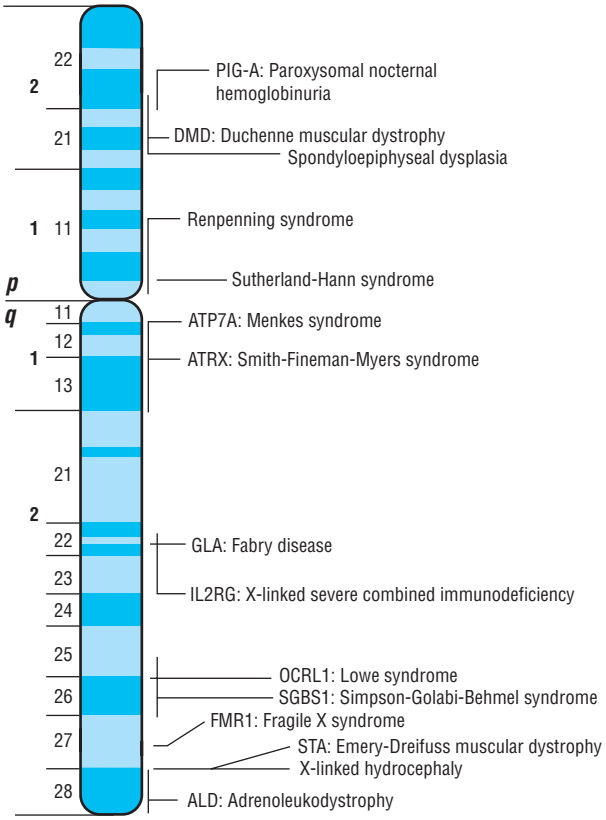
Chromosome 21



Chromosome 22



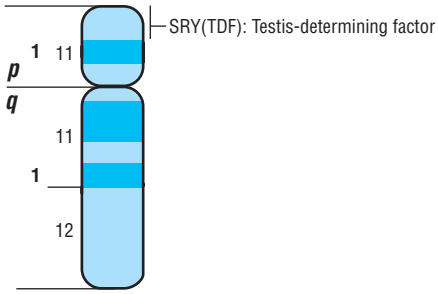
Chromosome X



Asplenia (x)

KAL: Kallman syndrome (x)

Chromosome Y



ORGANIZATIONS

The following is an alphabetical compilation of organizations listed in the *Resources* section of the main body entries. Although the list is comprehensive, it is by no means exhaustive. It is a starting point for further information, as well as other online and print sources. Many of the organizations listed provide information for multiple disorders and have links to additional related websites. E-mail addresses and web addresses listed were provided by the associations; Gale Group is not responsible for the accuracy of the addresses or the contents of the websites.

5p-Society
7108 Katella Ave. #502
Stanton, CA 90680
Phone: (888) 970-0777
Website: http://www.fivepminus.org

A

A-T Children's Project
668 South Military Trail
Deerfield Beach, FL 33442
Phone: (800) 5-HELP-A-T
Website: http://www.atcp.org

A-T Medical Research Foundation
5241 Round Meadow Road
Hidden Hills, CA 91302
Website: http://www.pathnet.medsch.ucla.edu/people/faculty/gatti/gatsign.htm

AboutFace International
123 Edwards Street, Suite 1003
Toronto, ON M5G 1E2
Canada
Phone: (800) 665-FACE
E-mail: info@aboutfaceinternational.org
Website: http://www.aboutfaceinternational.org

AboutFace USA
PO Box 458
Crystal Lake, IL 60014
Phone: (312) 337-0742 or (888) 486-1209
E-mail: aboutface2000@aol.com
Website: http://www.aboutface2000.org

Achromatopsia Network
C/O Frances Futterman
PO Box 214
Berkeley, CA 94701-0214
Website: http://www.achromat.org/how_to_join.html

Acid Maltase Deficiency Association (AMDA)
PO Box 700248
San Antonio, TX 78270-0248
Phone: (210) 494-6144 or (210) 490-7161
Fax: (210) 490-7161 or (210) 497-3810
Website: http://www.amda-pompe.org

Agenesis of the Corpus Callosum (ACC) Network
University of Maine
Merrill Hall, Room 18, 5749
Orono, ME 04469-5749
Phone: (207) 581-3119
E-mail: um-acc@maine.edu

Aicardi Syndrome Awareness and Support Group
29 Delavan Ave.
Toronto, ON M5P 1T2
Canada
Phone: (416) 481-4095

Aicardi Syndrome Foundation
450 Winterwood Dr.
Roselle, IL 60172
Phone: (800) 373-8518.
Website: http://www.aicardi.com

AIS Support Group (AISSG)
PO Box 269, Banbury
Oxon, OX15 6YT
United Kingdom
Website: http://www.medhelp.org/www/ais

AKU Hotline
Website: http://www.goodnet.com/~ee72478/enable/hotline.htm

Alcoholics Anonymous World Services
PO Box 459, Grand Central Station
New York, NY 10163
Phone: (212) 870-3400

Alexander Graham Bell Association for the Deaf, Inc.
3417 Volta Place NW
Washington, DC 20007-2778.
Phone: (800) 432-7543
Website: http://www.agbell.org

Allergy and Asthma Network. Mothers of Asthmatics, Inc.
2751 Prosperity Ave., Suite 150
Fairfax, VA 22031
Phone: (800) 878-4403
Fax: (703) 573-7794

Alliance of Genetic Support Groups
4301 Connecticut Ave. NW, Suite 404
Washington, DC 20008
Phone: (202) 966-5557
Fax: (202) 966-8553
Website: http://www.geneticalliance.org

Alpha 1 National Association
8120 Penn Ave. South, Suite 549
Minneapolis, MN 55431
Phone: (612) 703-9979 or (800) 521-3025
E-mail: julie@alpha1
Website: http://www.alpha1.org

Alpha One Foundation
2937 SW 27th Ave., Suite 302,
Miami, FL 33133.
Phone: (305) 567-9888 or (877) 228-7321.
E-mail: mserven@alphaone.
Website: http://www.alphaone.org

Alpha to Alpha
RR#5 Box 859
Warsaw, MO 65355
Phone: (660) 438-3045
Website: http://www.alpha2alpha.org

AlphaNet
Phone: (800) 557-2638
Website: http://www.alphanet.org

ALS Association of America (ALSA)
27001 Agoura Road, Suite 150
Calabasas Hills, CA 91301-5104
Phone: (818) 800-9006
Fax: (818) 880-9006
Website: http://www.alsa.org

Alzheimer's Association
919 North Michigan Ave., Suite 1000
Chicago, IL 60611-1676
Phone: (800) 272-3900

Alzheimer's Disease International
45/46 Lower Marsh
London, SE1 7RG
United Kingdom
Phone: (+44 20) 7620 3011
E-mail: adi@alz.co.uk
Website: http://www.alz.co.uk

Ambiguous Genitalia Support Network
PO Box 313
Clements, CA 95227-0313
Phone: (209) 727-0313
Fax: (209) 727-0313
E-mail: agsn@jps.net
Website: http://www.stepstn.com

AMD Alliance International
PO Box 550385
Atlanta, GA 30355
Phone: (877) 263-7171
Website: http://www.amdalliance.org

American Academy of Allergy, Asthma & Immunology
611 E. Wells Street
Milwaukee, WI 53202
Phone: (414) 272-6071
Fax: (414) 272-6070
Website: http://www.aaaai.org

American Academy of Dermatology
PO Box 4014, 930 N. Meacham Road
Schaumburg, IL 60168-4014
Phone: (847) 330-0230
Fax: (847) 330-0050
Website: http://www.aad.org

American Academy of Ophthalmology
PO Box 7424
San Francisco, CA 94120-7424
Phone: (415) 561-8500
Website: http://www.eyenet.org

American Academy of Pediatrics
141 Northwest Point Boulevard
Elk Grove Village, IL 60007-1098
Phone: (847) 434-4000
Fax: (847) 434-8000
Website: http://www.aap.org/visit/contact.htm

American Association for Klinefelter Syndrome Information and Support (AAKSIS)
2945 W. Farwell Ave.
Chicago, IL 60645-2925
Phone: (773) 761-5298 or (888) 466-5747
Fax: (773) 761-5298
E-mail: aaksis@aaksis.org
Website: http://www.aaksis.org

American Association for Pediatric Ophthalmology and Strabismus
Website: http://med-aapos.bu.edu/

American Association of the Deaf-Blind
814 Thayer Ave., Suite 302
Silver Spring, MD 20910
Phone: (301) 588-6545

American Association of Kidney Patients
100 S. Ashley Dr., Suite 280
Tampa, FL 33602
Phone: (800) 749-2257
Website: http://www.aakp.org

American Association on Mental Retardation (AAMR)
444 North Capitol Street NW, Suite 846
Washington, DC 20001-1512
Phone: (800) 424-3688.
Website: http://www.aamr.org

American Cancer Society
1599 Clifton Road NE
Atlanta, GA 30329
Phone: (800) 227-2345
Website: http://www.cancer.org

American Cleft Palate-Craniofacial Association
104 South Estes Dr., Suite 204
Chapel Hill, NC 27514
Phone: (919) 993-9044
Fax: (919) 933-9604
Website: http://www.cleftline.org

American College of Obstetricians and Gynecologists
PO Box 96920, 409 12th Street SW
Washington, DC 20090-6920
Website: http://www.acog.org

American College of Rheumatology
60 Executive Park South, Suite 150
Atlanta, GA 30329
Phone: (404) 633-3777
Website: http://www.rheumatology.org

American Council of the Blind
1155 15th Street NW, Suite 720
Washington, DC 20005
Phone: (202) 467-5081 or (800) 424-8666
Website: http://www.acb.org

American Diabetes Association
1701 N. Beauregard Street
Alexandria, VA 22311
Phone: (703) 549-1500 or (800) 342-2383
Website: http://www.diabetes.org

American Epilepsy Society
342 North Main Street
West Hartford, CT 06117
Phone: (860) 586-7505
Fax: (860 586-7550
E-mail: info@aesnet
Website: http://www.aesnet.org

American Foundation for the Blind
11 Penn Plaza, Suite 300
New York, NY 10001
Phone: (800) 232-5463

American Foundation for Urologic Disease, Inc.
1128 North Charles Street
Baltimore, MD 21201-5559
Phone: (410)468-1808
Website: http://www.afud.org

American Hair Loss Council
Phone: (888) 873-9719
Website: http://www.ahlc.org

American Heart Association
7272 Greenville Ave.
Dallas, TX 75231-4596
Phone: (214) 373-6300 or (800) 242-8721
E-mail: inquire@heart
Website: http://www.americanheart.org

American Hemochromatosis Society, Inc.
777 E. Atlantic Ave., PMB Z-363
Delray Beach, FL 33483-5352
Phone: (561) 266-9037 or (888) 655-IRON (4766)
E-mail: ahs@emi.net
Website: http://www.americanhs.org

American Kidney Fund
Suite 1010, 6110 Executive Boulevard
Rockville, MD 20852
Phone: (899) 638-8299

American Liver Foundation
75 Maiden Lane, Suite 603
New York, NY 10038

Phone: (800) 465-4837 or (888) 443-7222
Website: http://www.liverfoundation.org

American Lung Association
1740 Broadway
New York, NY 10019-4374
Phone: (212) 315-8700 or (800) 586-4872
Website: http;//www.lungusa.org

American Macular Degeneration Foundation
PO Box 515
Northampton, MA 01061-0515
Phone: (413) 268-7660
Website: http://www.macular.org

American Medical Association
Washington Office
1101 Vermont Ave. NW
Washington, DC 20005
Phone: (202) 789-7400
Website: http://www.ama-assn.org

American Nystagmus Network
PO Box 45
Jenison, MI 49429-0045
Website: http://www.nystagmus.org

American Optometric Association
243 North Lindbergh Boulevard
St. Louis, MO 63141
Phone: (314) 991-4100
Website: http://www.aoanet.org

American Porphyria Foundation
PO Box 22712
Houston, TX 77227
Phone: (713) 266-9617
Website: http://www.enterprise.net/apf/

American Pseudo-Obstruction & Hirschsprung's Society
158 Pleasant Street
North Andover, MA 01845
Phone: (978) 685-4477

American Psychiatric Association
1400 K Street NW
Washington, DC 20005
Phone: (202) 682-6220

American Sleep Disorders Association
1610 14th Street NW, Suite 300
Rochester, MN 55901
Phone: (507) 287-6006

American Society for Deaf Children
PO Box 3355
Gettysburg, PA 17325
Phone: (800) 942-ASDC or (717) 334-7922 v/tty
Website: http://www.deafchildren.org/asdc2k/home/home.shtml

American Society for Dermatologic Surgery
1567 Maple Ave.
Evanston, IL 60201
Phone: (708) 869-3954

American Society for Reproductive Medicine
1209 Montgomery Highway
Birmingham, AL 35216-2809
Phone: (205) 978-5000
E-mail: asrm@asrm
Website: http://www.asrm.org

American Society of Human Genetics
9650 Rockville Pike
Bethesda, MD 20814-3998
Phone: (301) 571-1825
Website: http://www.faseb.org/genetics/ashg/ashgmenu.htm

American Society of Hypertension
515 Madison Ave., Suite 1212
New York, NY 10022
Phone: (212) 644-0600
Website: http://www.ash-us.org

American Syringomelia Project
PO Box 1586
Longview, TX 75606-1586
Phone: (903) 236-7079

American Thyroid Association
PO Box 1836
Falls Church, VA 22041-1836
Phone: (410) 243-4483
Fax: (703) 998-8893
Website: http://www.thyroid.org

Anemia Institute for Research and Education
151 Bloor Street West, Suite 600
Toronto, ON M5S 1S4
Canada
Phone: (877) 99-ANEMIA
Website: http://www.anemiainstitute.net

Angelman Syndrome Foundation
414 Plaza Dr., Suite 209
Westmont, IL 60559-1265
Phone: (630) 734-9267 or (800) 432-6435
Fax: (630) 655-0391
E-mail: info@angelman
Website: http://www.angelman.org

Anxiety Disorders Association of America
11900 Parklawn Dr., Suite 100
Rockville, MD 20852
Phone: (301) 231-9350
Fax: (301) 231-7392
E-mail: anxdis@adaa.org

Apert Syndrome Support Group
8708 Kathy
St. Louis, MO 63126
Phone: (314) 965-3356

Aplastic Anemia Foundation
PO Box 613
Annapolis, MD 21404-0613
Phone: (800) 747-2820
Website: http://www.aplastic.org

Arc (A National Organization on Mental Retardation)
1010 Wayne Ave., Suite 650
Silver Spring, MD 20910
Phone: (800) 433-5255
Website: http://www.tharclink.org

Arc of the United States (formerly Association for Retarded Citizens of the US)
500 East Border Street, Suite 300
Arlington, TX 76010
Phone: (817) 261-6003
Website: http://thearc.org

Arc's Fetal Alcohol Syndrome Resource Guide
The Arc's Publication Desk
3300 Pleasant Valley Lane, Suite C,
Arlington, TX 76015
Phone: (888) 368-8009
Website: http://www.thearc.org/misc/faslist.html

Arthritis Foundation
1330 West Peachtree Street
Atlanta, GA 30309
Phone: (800) 283-7800
Website: http://www.arthritis.org

The Arthrogryposis Group (TAG)
1 The Oaks, Gillingham
Dorset, SP8 4SW
United Kingdom
Phone: 01-747-822655
Website: http://tagonline.org.uk

Association for Glycogen Storage Disease (United Kingdom)
Phone: 0131 554 2791
Fax: 0131 244 8926
Website: http://www.agsd.uk

Association for Macular Diseases, Inc.
210 East 64th Street
New York, NY 10021
Phone: (212) 605-3719
E-mail: 2020@nei.nih.gov
Website: http://www.macula@macula.org

Association for Neuro-Metabolic Disorders
5223 Brookfield Lane
Sylvania, OH 43560-1809
Phone: (419) 885-1497

Association for Science in Autism Treatment
175 Great Neck Road, Suite 406
Great Neck, NY 11021
Phone: (516) 466-4400
Fax: (516) 466-4484
E-mail: asat@autism-treatment

Association for Spina Bifida and Hydrocephalus
42 Park Road
Peterborough, PE1 2UQ
United Kingdom
Phone: 0173 355 5988
Fax: 017 3355 5985
E-mail: postmaster@asbah
Website: http://www.asbah.demon.co.uk

Association for the Bladder Exstrophy Community
PO Box 1472
Wake Forest, NC 27588-1472
Phone: (919) 624-9447
Website: http://www.bladderexstrophy.com/support.htm

Association of Birth Defects in Children
930 Woodcock Road, Suite 225
Orlando, FL 32803
Phone: (407) 895-0802
Website: http://www.birthdefects.org

Asthma and Allergy Foundation of America (AAFA)
1233 20th Street NW, Suite 402
Washington, DC 20036
Phone: (800) 7-ASTHMA
Fax: (202) 466-8940
Website: http://www.aafa.org

The A-T Project
3002 Enfield Road
Austin, TX 78703
Phone: (512) 472-4892
Website: http://www.atproject.org

Ataxia MJD Research Project, Inc.
875 Mahler Road, Suite 161
Burlingame, CA 94010-1621
Phone: (650) 259-3984
Fax: (650) 259-3983
Website: http://www.ataxiamjd.org

Autism Research Institute
4182 Adams Ave.
San Diego, 92116
Fax: (619) 563-6840

Autism Society of America
7910 Woodmont Ave. Suite 300
Bethesda, MD 20814-3015
Phone: (301) 657-0881 or (800) 3-AUTISM
Website: http://www.autism-society.org

AVENUES National Support Group for Arthrogryposis Multiplex Congenita
PO Box 5192
Sonora, CA 95370
Phone: (209) 928-3688
E-mail: avenues@sonnet.com
Website: http://www.sonnet.com/avenues

B

Bachmann-Strauss Dystonia & Parkinson Foundation, Inc.
Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1490
New York, NY 10029
Phone: (212) 241-5614
Website: http://www.dystonia-parkinsons.org

Battens Disease Support and Research Association
2600 Parsons Ave.
Columbus, OH 43207
Phone: (800) 448-4570
Website: http://www.bdsra.org

Beckwith-Wiedemann Support Network
2711 Colony Road
Ann Arbor, MI 48104
Phone: (734) 973-0263 or (800) 837-2976
Website: http://www.beckwith-wiedemann.org

Blind Children's Fund
4740 Okemos Road
Okemos, MI 48864-1637
Phone: (517) 347-1357
Website: http://www.blindchildrensfund.org

Boys Town National Research Hospital
555 N. 30th Street
Omaha, NE 68131
Phone: (402) 498-6749
Website: http://www.boystown.org/Btnrh/Index.htm

C

Canadian Hemophilia Society
625 President Kennedy, Suite 1210
Montreal, QUE H3A 1K2
Canada
Phone: (514) 848-0503
Fax: (514) 848-9661
E-mail: chs@hemophilia.ca
Website: http://www.hemophilia.ca/english/index.html

Canadian Multiple Endocrine Neoplasia Type 1 Society, Inc. (CMEN)
PO Box 100
Meota, SK S0M 1X0
Canada
Phone: (306) 892-2080

Canadian Opitz Family Network
Box 892
Errington, BC V0R 1V0
Canada
Phone: (250) 954-1434
Fax: (250) 954-1465
E-mail: opitz@apollos.net
Website: http://www.apollos.net/arena/opitz/start.html

Canadian Society for Mucopolysaccharide and Related Diseases
PO Box 64714
Unionville, ON L3R-OM9
Canada
Phone: (905) 479-8701 or (800) 667-1846
Website: http://www.mpssociety.ca

Canavan Foundation
320 Central Park West, Suite 19D
New York, NY 10025
Phone: (212) 877-3945

Canavan Research Foundation
Fairwood Professional Building
New Fairwood, CT 06812
Phone: (203) 746-2436
E-mail: canavan_research@hotmail.com
Website: http://www.canavan.org

Cardiac Arrhythmias Research and Education Foundation, Inc.
2082 Michelson Dr., #301
Irvine, CA 92612-1212
Phone: (949) 752-2273 or (800) 404-9500
E-mail: care@longqt
Website: http://www.longqt.org

Cardio-Facio-Cutaneous Support Network
157 Alder Ave.
McKee City, NJ 08232
Phone: (609) 646-5606

Cardio-Facio-Cutaneous Syndrome Family Network
183 Brown Road
Vestal, NY 13850
Phone: (607) 772-9666
Website: http://www.cfcsyndrome.org

Cardio-Facio-Cutaneous Syndrome Foundation
3962 Van Dyke Street
White Bear Lake, MN 55110
Website: http://www.cfcfoundation.com

Center for Loss in Multiple Birth, Inc. (CLIMB)
PO Box 1064
Palmer, AK 99654
Phone: (907) 222-5321

Center for Neurologic Study
9850 Genesee Ave., Suite 320
Lajolla, CA 92037
Phone: (858) 455-5463
Fax: (858) 455-1713
E-mail: cns@cts
Website: http://www.cnsonline.org

Center for Study of Multiple Birth
334 E. Superior Street, Suite 464
Chicago, IL 60611
Phone: (312) 266-9093
Website: http://www.multiplebirth.com

Centers for Disease Control
Office of Genetics and Disease Prevention
4770 Buford Highway NE
Atlanta, GA 30341-3724
Phone: (770) 488-3235
Fax: (770) 488-3236
E-mail: genetics@cdc.gov
Website: http://www.cdc.gov/genetics

Changing Faces
1 & 2 Junction Mews
London, W2 1PN
United Kingdom
Phone: 0207 706 4232
E-mail: info@changingfaces.co.uk
Website: http://www.changingfaces.co.uk

Charcot Marie Tooth Association (CMTA)
2700 Chestnut Parkway
Chester, PA 19013
Phone: (610) 499-9264 or (800) 606-CMTA
Fax: (610) 499-9267
E-mail: cmtassoc@aol.com
Website: http://www.charcot-marie-tooth.org

CHARGE Family Support Group
82 Gwendolen Ave.
London, E13 ORD
United Kingdom
Phone: 020-8552-6961
Website: http://www.widerworld.co.uk/charge

CHARGE Syndrome Foundation
2004 Parkade Boulevard
Columbia, MO 65202-3121
Phone: (800) 442-7604
Website: http://www.chargesyndrome.org

CHASER (Congenital Heart Anomalies Support, Education, and Resources)
2112 North Wilkins Road
Swanton, OH 43558
Phone: (419) 825-5575
Website: http://www.csun.edu/~hfmth006/chaser

Cherub Association of Families & Friends of Limb Disorder Children
8401 Powers Road
Batavia, NY 14020
Phone: (716) 762-9997

Children Living with Inherited Metabolic Diseases
The Quadrangle, Crewe Hall, Weston Road, Crewe
Cheshire, CW1-6UR
United Kingdom
Phone: 127 025 0221
Fax: 0870-7700-327
Website: http://www.climb.uk

Children's Blood Foundation
333 East 38th Street, Room 830
New York, NY 10016-2745
Phone: (212) 297-4336
E-mail: cfg@nyh.med.cornell.edu

Children's Brain Disease Foundation
350 Parnassus Ave., Suite 900
San Francisco, CA 94117
Phone: (415) 566-5402

Children's Brittle Bone Foundation
7701 95th Street
Pleasant Prairie, WI 53158
Phone: (847) 433-498
Website: http://www.cbbf.org

Children's Craniofacial Association
PO Box 280297
Dallas, TX 75243-4522
Phone: (972) 994-9902 or (800) 535-3643
E-mail: contactcca@ccakids.com
Website: http://www.ccakids.com

Children's Gaucher Research Fund
PO Box 2123
Granite Bay, CA 95746-2123
Phone: (916) 797-3700
Fax: (916) 797-3707
Website: http://www.childrensgaucher.org

Children's Mitochondrial Disease Network
Mayfield House, 30 Heber Walk, Chester Way,
Northwich, CW9 5JB
United Kingdom
Phone: 01606 44733
Website: http://www.emdn-mitonet.co.uk

Choroideremia Research Foundation
23 E. Brundreth Street
Springfield, MA 01109
Website: http://www.choroideremia.org

Chromosome 18 Registry and Research Society
6302 Fox Head
San Antonio, TX 78247
Phone: (210) 567-4968
Website: http://www.chromosome18.org

Chromosome Deletion Outreach, Inc.
PO Box 724
Boca Raton, FL 33429-0724
Phone: (561) 391-5098 or (888) 236-6880
Fax: (561) 395-4252
E-mail: cdo@worldnet.att.net
Website: http://members.aol.com/cdousa/cdo.htm

CMT International
Attn: Linda Crabtree
1 Springbank Dr.
St. Catherine's, ON L2S2K1
Canada
Phone: (905) 687-3630
Website: http://www.cmtint.org

Coalition for Heritable Disorders of Connective Tissue (CHDCT)
382 Main Street
Port Washington, NY 11050
Phone: (516) 883-8712
Website: http://www.chdct.org

Colon Cancer Alliance
175 Ninth Ave
New York, NY 10011
Phone: (212) 627-7451
Website: http://ccalliance.org

Colorectal Cancer Network
PO Box 182
Kensington, MD 20895-0182
Phone: (301) 879-1500
Website: http://www.colorectal-cancer.net

Columbia Presbyterian Medical Center
Dept. of Neurological Surgery
710 West 168 Street
New York, NY 10032
Phone: (212) 305-0378
Fax: (212) 305-3629
Website: http://cpmcnet.columbia.edu/dept/nsg/PNS/Hydrocephalus.html

Congenital Heart Anomalies Support, Education, and Resources
2112 North Wilkins Road
Swanton, OH 43558
Phone: (419) 825-5575
Website: http://www.csun.edu/~hfmth006/chaser

Congenital Heart Disease Information and Resources
1561 Clark Dr.
Yardley, PA 19067
Website: http://www.tchin.org

Conjoined Twins International
PO Box 10895
Prescott, AZ 86304-0895

Cooley's Anemia Foundation, Inc.
129-09 26th Ave. #203
Flushing, NY 11354
Phone: (800) 522-7222 or (718) 321-2873
Website: http://www.thalassemia.org

Cornelia de Lange Syndrome Foundation, Inc.
302 West Main Street, Suite 100
Avon, CT 06001
Phone: (860) 676-8166 (800) 223-8355
Fax: (860) 676-8337

Corporation for Menkes Disease
5720 Buckfield Court
Fort Wayne, IN 46814
Phone: (219) 436-0137

Council of Regional Networks for Genetic Services
Genetic Services Program, Wadsworth Center Labs & Research
PO Box 509, Room E299, Empire State Plaza
Albany, NY 12201-0509
Phone: (518) 474-7148
Website: http://www.cc.emory.edu/PEDIATRICS/corn/corn.htm

Craniosynostosis and Parents Support (CAPS)
2965-A Quarters
Quantico, VA 22134
Phone: (877) 686-CAPS or (703) 445-1078
Website: http://www.caps2000.org/

Creutzfeldt-Jakob Disease Foundation, Inc.
PO Box 611625
Miami, FL 33261-1625
Fax: (954) 436-7591
Website: http://www.cjdfoundation.org

Cri du Chat Society
Dept. of Human Genetics, Box 33, MCV Station,
Richmond VA 23298
Phone: (804) 786-9632

Cri du Chat Syndrome Support Group
Website: http://www.cridchat.u-net.com

Crouzon Support Network
PO Box 1272
Edmonds, WA 98020
E-mail: penny@crouzon
Website: http://www.crouzon.org

Crouzon's/Meniere's Parent Support Network
3757 North Catherine Dr.
Prescott Valley, AZ 86314-8320
Phone: (800) 842-4681
E-mail: katy@northlink.com

Cure Autism Now (CAN) Foundation
5455 Wilshire Boulevard Suite 715
Los Angeles, CA 90036-4234
Phone: (500) 888-AUTISM
Fax: (323) 549-0547
E-mail: info@cureautismnow
Website: http://www.cureautismnow.org

Cystic Fibrosis Foundation
6931 Arlington Road
Bethesda, MD 20814
Phone: (301) 951-4422
Website: http://www.cff.org

Cystinosis Foundation
2516 Stockbridge Dr.
Oakland, CA 94611
Phone: (800) 392-8458
Website: http://www.cystinosisfoundation.org

Cystinosis Research Network
8 Sylvester Road
Burlington, MA 01803
Phone: (866) CURE NOW
Fax: (781) 229-6030
Website: http://www.cystinosis.org

D

Dandy-Walker Syndrome Network
5030 142nd Path West
Apple Valley, MN 55124
Phone: (612) 423-4008

DB-LINK, Teaching Research
345 N. Monmouth Ave.
Monmouth, OR 97361.
Phone: (800) 438-9376.
Website: http://www.tr.wou.edu/dblink/about.htm

Deafness Research Foundation
575 Fifth Ave., 11th Floor
New York, NY 10017
Phone: (800) 535-3323
E-mail: drf@drf

Diabetes Action Research and Education Foundation
426 C Street NE
Washington, DC 20002
Website: http://www.daref.org

Dubowitz Syndrome Nationwide Support Group Network
RR 1 Box 114
Downs, IL 61736
Phone: (309) 724-8407

Dubowitz Syndrome Parent Support
PO Box 173
Wheatland, IN 47597
Phone: (812) 886-0575

Dysautonomia Foundation, Inc.
633 Third Ave., 12th Floor
New York, NY 10017-6706
Phone: (212) 949-6644

Website: http://www.med.nyu.edu/fd/fdcenter.html

Dystonia Medical Research Foundation
One East Wacker Dr., Suite 2430
Chicago, IL 60601
Phone: (312) 755-0198
Website: http://www.dystonia-foundation.org

Dystrophic Epidermolysis Bullosa Research Association of America (DebRA)
40 Rector Street, Suite 1403
New York, NY 10006
Phone: (212) 513-4090
Fax: (212) 513-4099
E-mail: staff.debra@exario.net
Website: http://www.debra.org

Dystrophic Epidermolysis Bullosa Research Association of United Kingdom, (DebRA)
13 Wellington Business Park
Dukes Ride, Crowthorne
Berkshire, RG45 6LS
United Kingdom
Phone: 011-01344 771961
E-mail: admin@debra.uk
Website: http://www.debra.org.uk

E

EA/TEF Child and Family Support Connection, Inc.
111 West Jackson Boulevard, Suite 1145
Chicago, IL 60604-3502
Phone: (312) 987-9085
Fax: (312) 987-9086
E-mail: eatef2@aol.com
Website: http://www.eatef.org/

EAR (Education and Auditory Research) Foundation
1817 Patterson Street
Nashville, TN 37203
Phone: (800) 545-HEAR
E-mail: earfound@earfoundation
Website: http://www.theearfound.org

Ectodermal Dyplasia Society
108 Charlton Lane
Cheltenham, GlosGL53 9EA
United Kingdom
Website: http://www.ectodermaldysplasia.org

Ehlers-Danlos Support Group—UK
PO Box 335, Farnham
Surrey, GU10 1XJ
United Kingdom
Phone: 01252 690 940
Website: http://www.atv.ndirect.co.uk

Elhers-Danlos National Foundation
6399 Wilshire Boulevard, Suite 203
Los Angeles, CA 90048
Phone: (323) 651-3038
Fax: (323) 651-1366
Website: http://www.ednf.org

Ellis-Van Creveld Foundation
Farthingdale Farm, Hackmans Lane, Purleigh
Chelmsford, CM3 6RW
United Kingdom
Phone: 01-621-829675
Website: http://www.cafamily.uk/Direct/e24.html

Endocrine Society
4350 East West Highway, Suite 500
Bethesda, MD 20814-4410
Phone: (301) 941-0200
Fax: (301) 941-0259
E-mail: endostaff@endo-society.

Epilepsy Foundation of America
4351 Garden City Dr., Suite 406
Landover, MD 20785-2267
Phone: (301) 459-3700 or (800) 332-1000
Website: http://www.epilepsyfoundation.org

European Chromosome 11q Network
Attn: Annet van Betuw
Else Mauhsstraat 7
6708 NJ Wageningen
Netherlands
Phone: (+31) 317-42 33 45
Fax: (+31) 317-42 69 80
Website: http://www.11q.org

European Long QT Syndrome Information Center
Ronnerweg 2
Nidau, 2560
Switzerland
Phone: 04(132) 331-5835
E-mail: jmettler@bielnews.ch
Website: http://www.bielnews.ch/cyberhouse/qt/qt.html

Eye Bank Association of America
1015 18th Street NW, Suite 1010
Washington, DC 20036
Phone: (202) 775-4999
Website: http://www.restoresight.org/

Eye Cancer Network
115 East 61st Street
New York, NY 10021
Phone: (212) 832-8170
Website: http://www.eyecancer.com

F

Fabry Support and Information Group
PO Box 510, 108 NE 2nd Street, Suite C
Concordia, MO 64020
Phone: (660) 463-1355
Website: http://www.cpgnet.com/fsig.nsf

FACES. The National Craniofacial Assocation
PO Box 11082
Chattanooga, TN 37401
Phone: (423) 266-1632 or (800) 332-2373
E-mail: faces@faces-cranio.
Website: http://www.faces-cranio.org/

FacioScapuloHumeral Society, Inc.
3 Westwood Road
Lexington, MA 02420
Phone: (781) 860-0501
E-mail: carol.perez@fshsociety
Website: http://www.fshsociety.org

Factor V Leiden
Website: http://www.fvleiden.org

Families of Adults Afflicted with Asperger's Syndrome (FAAAS)
PO Box 514
Centerville, MA 02632
Website: http://www.faaas.org

Families with Moyamoya Support Network
4900 McGowen Street SE
Cedar Rapids, IA 54203

Family Village
University of Wisconsin-Madison, Waisman Center
1500 Highland Ave.
Madison, WI 53705-2280
E-mail: familyvillage@waisman.wisc.edu
Website: http://www.familyvillage.wisc.edu/index.html

Fanconi Anemia Research Fund
1801 Willamette Street, Suite 200
Eugene, OR 97401-4030
Phone: (800) 828-4891
Website: http://www.fanconi.org

Fatty Oxidation Disorders (FOD) Family Support Group
Deb Lee Gould, MEd, Director, FOD Family Support Group, MCAD Parent and Grief Consultant
805 Montrose Dr.

Greensboro, NC 24710
Phone: (336) 547-8682
Website: http://www.fodsupport.org

Fetal Alcohol Syndrome Family Resource Institute
PO Box 2525
Lynnwood, WA 98036
Phone: (253) 531-2878 or (800) 999-3429
Website: http://www.fetalalcoholsyndrome.org

Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
Phone: (888) 463-6332
Website: http://www.fda.gov

Footsteps Institute for Rare Diseases
624 Martin Luther King Way
Tacoma, WA 98405
Phone: (253) 383-0985 or (888) 640-4673
E-mail: rwrfsi@aol.com

Forbes Norris ALS Research Center
California Pacific Medical Center
2324 Sacramento Street
San Francisco, CA 94115
Phone: (415) 923-3604
Fax: (415) 673-5184

Forward Face, Inc.
317 East 34th Street, Room 901
New York, NY 10016
Phone: (212) 684-5860 or (800) 393-3223

Foundation Fighting Blindness
Executive Plaza 1, Suite 800, 11350 McCormick Road
Hunt Valley, MD 21031
Phone: (888) 394-3937
Website: http://www.blindness.org

Foundation for Blood Research
PO Box 190, 69 US Route One
Scarborough, ME 04070-0190
Phone: (207) 883-4131
Fax: (207) 883-1527
Website: http://www.fbr.org

Foundation for Ichthyosis and Related Skin Types
650 N. Cannon Ave., Suite 17
Landsdale, PA 19446
Phone: (215) 631-1411 or (800) 545-3286
Fax: (215) 631-1413
Website: http://www.scalyskin.org

Foundation for Osteoporosis Research and Education
300 27th Street
Oakland, CA 94612
Phone: (888) 266-3015
Website: http://www.fore.org

Freeman-Sheldon Parent Support Group
509 East Northmont Way
Salt Lake City, UT 84103-3324
Phone: (801) 364-7060

Friedreich's Ataxia Research Alliance
2001 Jefferson Davis Highway #209
Arlington, VA 22202
Phone: (703) 413-4468
Website: http://www.frda.org

G

GeneTests
Children's Hospital and Regional Medical Center
PO Box 5371
Seattle, WA 98105-0371
Phone: (206) 527-5742
Fax: (206) 527-5743
Website: http://www.genetests.org/

Genetic Alliance
4301 Connecticut Ave. NW, #404
Washington, DC 20008-2304
Phone: (202) 966-5557
Helpline: (800) 336-GENE
Fax: (888) 394-3937
E-mail: info@geneticalliance
Website: http://www.geneticalliance.org

Glanzmann's Thrombasthenia Support Group
28 Duke Road, Newton
Hyde, SK14 4JB
United Kingdom
Phone: 0161-368-0219

Glaucoma Foundation
33 Maiden Lane
New York, NY 10038
Phone: (800) 452-8266
Website: http://www.glaucoma-foundation.org

Glaucoma Research Foundation
200 Pine Street, Suite 200
San Francisco, CA 94104
Phone: (800) 826-6693

Global Initiative for Asthma
Tim Clark, Chairman of GINA
Phone: (207) 594-5008
Fax: (207) 594-8802
E-mail: shurd@prodigy.net
Website: http://www.ginasthma.com

Goldenhar Parent Support Network
Attn: Kayci Rush
3619 Chicago Ave.
Minneapolis, MN 55407-2603
Phone: (612) 823-3529

Goldenhar Syndrome Research & Information Fund
PO Box 61643
St. Petersburg, FL 3371
Phone: (813) 522-5772
Website: http://www.goldenhar.com

Goldenhar Syndrome Support Network
9325 163 Street
Edmonton, ALB T5R 2P4
Canada
Website: http://i.am/bbds.page

Greenberg Center for Skeletal Dysplasias
600 North Wolfe Street, Block 1012C
Baltimore, MD 21287-4922
Phone: (410) 614-0977
Website: http://www.med.jhu.edu/Greenberg.Center/Greenbrg.htm

Guardians of Hydrocephalus Research Foundation
2618 Avenue Z
Brooklyn, NY 11235-2023
Phone: (718) 743-4473 or (800) 458-865
Fax: (718) 743-1171
E-mail: guardians1@juno.com

H

Haemophelia Society—von Willebrand Support Services
Chesterfield House, 385 Euston Road
London, NW1 3AU
United Kingdom
Phone: 0171 380 0600
Fax: 0171 387 8220
E-mail: melissa@haemophilia-soc.demon.co.uk
Website: http://www.haemophilia-soc.demon.co.uk/vwd%20services1.html

Headlines: the Craniofacial Support Group
Website: http://www.headlines.org.uk

Helen Keller National Center for Deaf-Blind Youths and Adults
111 Middle Neck Road
Sands Point, NY 11050
Phone: (516) 944-8900
Website: http://www.helenkeller.org/national/index.htm

Hemochromatosis Foundation, Inc.
PO Box 8569
Albany, NY 12208-0569
Phone: (518) 489-0972
E-mail: s.kleiner@shiva.hunter.cuny.edu.
Website: http://www.hemochromatosis.org

Hereditary Angioedema Association
PO Box 492
Live Oak, FL 32064
Website: http://www.hereditaryangioedema.com

Hereditary Colon Cancer Association (HCCA)
3601 N 4th Ave., Suite 201
Sioux Falls, SD 57104
Phone: (800) 264-6783
Website: http://hereditarycc.org

Hermansky-Pudlak Syndrome Network
39 Riveria Court
Malverne, NY 11565-1602
Phone: (800) 789-9477 or (516) 599-2077
Website: http://www.medhelp.org/web/hpsn.htm

Hermaphrodite Education and Listening Post
PO Box 26292
Jacksonville, NY 32226
E-mail: help@jaxnet.com
Website: http://users.southeast.net/~help/

Human BSE Foundation (United Kingdom)
Phone: 0191 389 4157
E-mail: humanbse.foundation@virgin.net

Human Growth Foundation
997 Glen Cove Ave.
Glen Head, NY 11545
Phone: (800) 451-6434
Fax: (516) 671-4055
Website: http://www. hgf1@hgfound.org

Hunter's Hope Foundation
PO Box 643
Orchard Park, NY 14127
Phone: (877) 984-HOPE
Fax: (716) 667-1212
Website: http://www.huntershope.org

Hydrocephalus Association
870 Market Street, Suite 705
San Francisco, CA 94102
Phone: (415) 732-7040 or (888) 598-3789
Fax: (415) 732-7044.
E-mail: hydroassoc@aol.com
Website: http://www.hydroassoc.org

Hydrocephalus Foundation, Inc. (HyFI)
910 Rear Broadway
Saugus, MA 01906
Phone: (781) 942-1161
E-mail: HyFI1@netscape.net
Website: http://www.hydrocephalus.org

Hydrocephalus Support Group, Inc.
PO Box 4236
Chesterfield, MO 63006-4236
Phone: (314) 532-8228
E-mail: hydrobuff@postnet.com

Hypospadias Association of America
4950 S. Yosemite Street, Box F2-156
Greenwood Village, CO 80111
E-mail: hypospadiasassn@yahoo.com
Website: http://www.hypospadias.net

I

Immune Deficiency Foundation
40 W. Chesapeake Ave., Suite 308
Towson, MD 21204
Phone: (800) 296-4433
Fax: (410) 321-9165
Website: http://www.primaryimmune.org

IMPACC (Intestinal Multiple Polyposis and Colorectal Cancer)
PO Box 11
Conyngham, PA 18219
Phone: (570) 788-1818

Inherited High Cholesterol Foundation
University of Utah School of Medicine
410 Chipeta Way, Room 167
Salt Lake City, UT 84104
Phone: (888) 244-2465

International Center for Fabry Disease
Department of Human Genetics
Box 1497, Fifth Ave. at 100th Street
New York, NY 10029
Phone: (866) 322-7963
Website: http://www.mssm.edu/genetics/fabry

International Patient Advocacy Association
800 Bellevue Way NE, Suite 400
Bellvue, WA 98004
Phone: (425) 462-4037 or (310) 229-5750 or (800) 944-7823 x4037
E-mail: lvp.ipaa@att.net
Website: http://www.vanpelt-ipaa.com

International Albinism Center
University of Minnesota
PO Box 420, Delaware Street SE
Minneapolis, MN 55455
Website: http://www.cbc.umn.edu/iac

International Center for Skeletal Dysplasia
Saint Joseph's Hospital
7620 York Road
Towson, MD 21204
Phone: (410) 337-1250

International Cohen Syndrome Support Group
7 Woods Court, Brackley
Northants, NN13-6HP
United Kingdom
Phone: (012) 80-704515

International Colour Vision Society: Forschungsstelle fuer Experimentelle Ophthalmologie
Roentgenweg 11
Tuebingen, D-72076
Germany
Website: http://orlab.optom.unsw.edu.au/ICVS

International Joseph Disease Foundation, Inc.
PO Box 2550
Livermore, CA 94551-2550
Phone: (925) 461-7550
Fax: (925) 371-1288
Website: http://www.ijdf.net

International Lesch-Nyhan Disease Association
114 Winchester Way
Shamong, NJ 08088-9398
Phone: (215) 677-4206

International Myopia Prevention Association
RD No. 5, Box 171
Ligonier, PA 15658
Phone: (412) 238-2101

International Patient Advocacy Association
800 Bellevue Way NE, Suite 400

Bellevue, WA 98004
Phone: (800) 944-7823 or (425) 462-4037
Fax: (425) 462-9532
E-mail: lvp.ipaa@att.net
Website: http://www.vanpelt-ipaa.com

International Peutz-Jeghers Support Group
Johns Hopkins Hospital
600 North Wolfe Street, Blalock 1008
Baltimore, MD 21287-4922

International Prader-Willi Syndrome Organization
Bizio 1, 36023 Costozza
Vicenza, Italy
Phone: +39 0444 555557
Fax: +39 0444 555557
Website: http://www.ipwso.org

International Progeria Registry
IBR Department of Human Genetics
1050 Forest Hill Road
Staten Island, NY 10314
Phone: (718) 494-5333
E-mail: wtbibr@aol.com

International Registry of Werner Syndrome
University of Washington
Department of Pathology
Health Science Bldg K543, Box 357470
Seattle, WA 98195
Phone: (206) 543-5088
Website: http://www.pathology.washington.edu/werner/registry/frame2.html

International Rett Syndrome Association
9121 Piscataway Road
Clinton, MD 20735
Phone: (800) 818-RETT
Website: http://www.rettsyndrome.org

International Society for Mannosidosis and Related Diseases
3210 Batavia Ave.
Baltimore, MD 21214
Phone: (410) 254-4903
E-mail: info@mannosidosis
Website: http://www.mannosidosis.org

Intersex Society of North America
PO Box 301
Petaluma, CA 94953-0301
Website: http://www.isna.org

Irish Raynaud's and Scleroderma Society
PO Box 2958 Foxrock
Dublin 18
Ireland
Phone: (01) 235 0900
E-mail: irss@indigo.ie

Iron Disorders Institute, Inc.
PO Box 3021
Greenville, SC 29602
Phone: (864) 241-0111
E-mail: irondis@aol.com
Website: http://www.irondisorders.org

Iron Overload Diseases Association, Inc.
433 Westwind Dr.
North Palm Beach, FL 33408
Phone: (561) 840-8512
E-mail: iod@ironoverload

Ivemark Syndrome Association
52 Keward Ave., Wells
Somerset, BAS-1TS
United Kingdom
Phone: 1-(74)967-2603

J

JNCL Research Fund
PO Box 766
Mundelein, IL 60060
Website: http://www.jnclresearch.org

Joubert Syndrome Foundation Corporation
Attn: Stephanie Frazer
384 Devon Drive
Mandeville, LA 70448

Juvenile Diabetes Foundation International (JDF)
120 Wall Street
New York, NY 10005
Phone: (212) 785-9500 x708 or (800) 533-2873
Website: http://www.jdf.org

K

Kabuki Syndrome Network
168 Newshaw Lane, Hadfield
Glossop, SK13 2AY
United Kingdom
Phone: 01457 860110
Website: http://www.ksn-support.uk

Kids with Heart
1578 Careful Dr.
Green Bay, WI 54304
Phone: (800) 538-5390
Website: http://www.execpc.com/~kdswhrt

KidsHealth. Nemours Center for Children's Health Media
PO Box 269
Wilmington, DE 19899
Website: http://www.kidshealth.org/teen/health_problems/diseases/asthma.html

Klinefelter Syndrome and Associates, Inc.
PO Box 119
Roseville, CA 95678-0119
Phone: (916) 773-2999 or (888) 999-9428
Fax: (916) 773-1449
E-mail: ksinfo@genetic
Website: http://www.genetic.org/ks

Klinefelter's Organization
PO Box 60
Orpington, BR68ZQ
United Kingdom
Website: http://hometown.aol.com/KSCUK/index.htm

Klippel-Trenaunay Support Group
5404 Dundee Road
Edina, MN 55436
Phone: (612) 925-2596

L

Lactic Acidosis Support Trust
1A Whitley Close, Middlewich
Cheshire, CW10 0NQ
United Kingdom
Phone: (016) 068-37198

Langer-Giedion Syndrome Association
89 Ingham Ave.
Toronto, ON M4K 2W8
Canada
Phone: (416) 465-3029
E-mail: kinross@istar.ca

League for the Hard of Hearing
71 West 23rd Street
New York, NY 10010
Phone: (917) 305-7700 or (917) 305-7999
Fax: (917) 305-7888
Website: http://www.lhh.org/index.htm

Lesch-Nyhan Syndrome Registry
New York University School of Medicine
Department of Psychiatry
550 First Ave.

New York, NY 10012
Phone: (212) 263-6458

Let's Face It (USA)
PO Box 29972
Bellingham, WA 98228-1972
Phone: (360) 676-7325
E-mail: letsfaceit@faceit
Website: http://www.faceit.org/letsfaceit

Leukemia Research Fund
43 Great Ormond St
London, WC1N 3JJ
England
Phone: 020-7405-3139
Website: http://dspace.dial.pipex.com/lrf

Leukemia & Lymphoma Society
1311 Mamaroneck Ave.
White Plains, NY 10605
Phone: (914) 949-5213
Website: http://www.leukemia-lymphoma.org

Lissencephaly Network, Inc.
716 Autumn Ridge Lane
Fort Wayne, IN 46804-6402
Phone: (219) 432-4310
Fax: (219) 432-4310
E-mail: lissennet@lissencephaly
Website: http://www.lissencephaly.org

Little People of America, Inc.
National Headquarters
PO Box 745
Lubbock, TX 79408
Phone: (806) 737-8186 or (888) LPA-2001
E-mail: lpadatabase@juno.com
Website: http://www.lpaonline.org

Little People's Research Fund, Inc.
80 Sister Pierre Dr.
Towson, MD 21204-7534
Phone: (410) 494-0055 or (800) 232-5773
Fax: (410) 494-0062
Website: http://pixelscapes.com/lprf

Lowe Syndrome Association
222 Lincoln Street
West Lafayette, IN 47906-2732
Phone: (765) 743-3634
Website: http://www.lowesyndrome.org

M

Macular Degeneration Foundation
PO Box 9752
San Jose, CA 95157
Phone: (888) 633-3937
Website: http://www.eyesight.org

MAGIC Foundation for Children's Growth
1327 N. Harlem Ave.
Oak Park, IL 60302
Phone: (708) 383-0808 or (800) 362-4423
Fax: (708) 383-0899
E-mail: mary@magicfoundation
Website: http://www.magicfoundation.org/ghd.html

Malignant Hyperthermia Association of the United States
PO Box 1069, 39 East State Street
Sherburne, NY 13460
Phone: (800) 98-MHAUS
Website: http://www.mhaus.org

March of Dimes Birth Defects Foundation
1275 Mamaroneck Ave.
White Plains, NY 10605
Phone: (888) 663-4637.
E-mail: resourcecenter@modimes
Website: http://www.modimes.org

McKusick Nathans Institute of Genetic Medicine
Johns Hopkins University
600 North Wolfe Street, Blalock 1008
Baltimore, MD 21287-4922
Phone: (410) 955-3071

Meckel-Gruber Syndrome Foundation
Website: http://www.meckel-gruber.org

Metabolic Information Network
PO Box 670847
Dallas, TX 75367-0847
Phone: (214) 696-2188 or (800) 945-2188

MHE and Me—A Support Group for Kids with Multiple Hereditary Exostoses
14 Stony Brook Dr.
Pine Island, NY 10969
Phone: (914) 258-6058
Website: http://www.geocities.com/mheandme

MJD Family Network Newsletter
c/o Mike and Phyllis Cote
591 Federal Furnace Road
Plymouth, MA 02360-4761

Möebius Syndrome Foundation (MSF)
PO Box 993
Larchmont, NY 10538
Phone: (914)834-6008
Website: http://www.ciaccess.com/moebius

Mucolipidosis IV Foundation
719 East 17th Street
Brooklyn, NY 11230
Phone: (718) 434-5067
Website: http://www.ML4.org

Multiple Hereditary Exostoses Coalition
8838 Holly Lane
Olmstead Falls, OH 44138
Phone: (440) 235-6325
Website: http://www.radix.net/~hogue/mhe.htm

Multiple Hereditary Exostoses Family Support Group
5316 Winter Moss Court
Columbia, MD 21045
Phone: (410) 922-5898
Website: http://www.radix.net/~hogue/mhe.htm

MUMS. National Parent to Parent Organization
150 Custer Court
Green Bay, WI 54301-1243
Phone: (920) 336-5333
Website: http://www.netnet.net/mums

Muscular Dystrophy Association—Canada
2345 Yonge Street, Suite 900
Toronto, ON M4P 2E5
Canada
Phone: (416) 488-2699
E-mail: info@mdac.ca
Website: http://www.mdac.ca/main.html

Muscular Dystrophy Association
3300 East Sunrise Dr.
Tucson, AZ 85718
Phone: (520) 529-2000 or (800) 572-1717
Website: http://www.mdausa.org

Muscular Dystrophy Campaign
7-11 Prescott Place
London, SW4 6BS
England
Phone: +44(0) 7720 8055
E-mail: info@muscular-dystrophy
Website: http://www.muscular-dystrophy.org

Muscular Dystrophy Family Foundation
615 North Alabama Street, Suite 330
Indianapolis, IN 46204-1213

Phone: (317) 632-8255 or (800) 544-1213
E-mail: mdff@prodigy.net
Website: http://www.mdff.org

Myasthenia Gravis Foundation of America
5841 Cedar Lake Road, Suite 204
Minneapolis, MN 55416
Phone: (800) 541-5454
Fax: (952) 545-6073

Myopia International Research Foundation
1265 Broadway, Room 608
New York, NY 10001
Phone: (212) 684-2777

N

Narcolepsy Network
PO Box 42460
Cincinnati, OH 45242
Phone: (973) 276-0115

National Adrenal Diseases Foundation
510 Northern Boulevard
Great Neck, NY 11021
Phone: (516) 487-4992
Website: http://medhlp.netusa.net/www/nadf.htm

National Alliance for Autism Research (NAAR)
414 Wall Street Research Park
Princeton, NJ 08540
Phone: (609) 430-9160 or (888) 777-6227 CA: (310) 230-3568
Fax: (609) 430-9163
Website: http://www.naar.org

National Alliance for the Mentally Ill
Colonial Place Three, 2107 Wilson Boulevard, Suite 300
Arlington, VA 22201
Phone: (703) 524-7600
HelpLine: (800) 950-NAMI
Website: http://www.nami.org/

National Alopecia Areata Foundation (NAAF)
PO Box 150760
San Rafael, CA 94915-0760
Phone: (415) 456-4644

National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse
One AMS Circle
Bethesda, MD 20892-3675
Phone: (301) 495-4484

National Association for Parents of Children with Visual Impairment (NAPVI)
PO Box 317
Watertown, MA 02472
Phone: (617) 972-7441 or (800) 562-6265
Website: http://www.spedex.com/napvi

National Association for Parents of the Visually Impaired
PO Box 317
Watertown, MA 02472
Phone: (617) 972-7441 or (800) 562-6265
Website: http://www.spedex.com/napvi

National Association for Visually Handicapped
22 West 21st Street
New York, NY 10010
Phone: (212) 889-3141
Website: http://www.navh.org

National Association of the Deaf
814 Thayer, Suite 250
Silver Spring, MD 20910-4500
Phone: (301) 587-1788
E-mail: nadinfo@nad
Website: http://www.nad.org

National Asthma Education and Prevention Program (NAEPP)
School Asthma Education Subcommittee
Website: http://www.nih.gov/health/asthma/index.htm

National Ataxia Foundation
2600 Fernbrook Lane, Suite 119
Minneapolis, MN 55447
Phone: (763) 553-0020
Fax: (763) 553-0167
E-mail: naf@ataxia
Website: http://www.ataxia.org

National Attention Deficit Disorder Association
1788 Second Street, Suite 200
Highland Park, IL 60035
Phone: (847) 432-ADDA

National Birth Defects Prevention Network
Atlanta, GA
Phone: (770) 488-3550
Website: http://www.nbdpn.org

National Cancer Institute
Office of Communications
31 Center Dr. MSC 2580, Bldg. 1 Room 10A16
Bethesda, MD 20892-2580
Phone: (800) 422-6237
Website: http://www.nci.nih.gov

National Center for Biotechnology Information
National Library of Medicine
Building 38A, Room 8N805
Bethesda, MD 20894
Phone: (301) 496-2475
Website: http://www3.ncbi.nlm.nih.gov

National Center for Environmental Health
Centers for Disease Control and Prevention
Mail Stop F-29
4770 Buford Highway NE
Atlanta, GA 30341-3724
Website: http://www.cdc.gov/nceh/asthma/default.htm

National Center for Health Statistics
Division of Data Services
6525 Belcrest Road
Hyattsville, MD 20782-2003
Website: http://www.cdc.gov/nchs

National Center on Sleep Disorders Research
Two Rockledge Centre
6701 Rockledge Dr.
Bethesda, MD 20892
Phone: (301) 435-0199

National Cholesterol Education Program
National Heart, Lung and Blood Institute
PO Box 30105
Bethesda, MD 20824
Phone: (301) 592-8573
Website: http://www.nhlbi.nih.gov

National Clearinghouse for Alcohol and Drug Information
PO Box 2345
Rockville, MD 20847
Phone: (800) 729-6686

National Council on Alcoholism and Drug Dependence Hopeline
12 West 21st Street
New York, NY 10010
Phone: (800) 622-2255

National Depressive and Manic Depressive Association
730 N. Franklin, Suite 501
Chicago, IL 60610-7204
Phone: (800) 826-3632 or (312) 642-7243
Website: http://www.ndmda.org

National Down Syndrome Congress
7000 Peachtree-Dunwoody Road, Bldg 5, Suite 100
Atlanta, GA 30328-1662
Phone: (770) 604-9500 or (800) 232-6372

Fax: (770) 604-9898
E-mail: ndsccenter@aol.com
Website: http://www.ndsccenter.org

National Down Syndrome Society
666 Broadway
New York, NY 10012-2317
Phone: (212) 460-9330 or (800) 221-4602
Fax: (212) 979-2873
E-mail: info@ndss.org
Website: http://www.ndss.org

National Easter Seal Society
230 W. Monroe Street, Suite 1800
Chicago, IL 60606-4802
Phone: (312) 726-6200 or (800) 221-6827
Website: http://www.easter-seals.org

National Epidermolysis Bullosa Registry
University of North Carolina at Chapel Hill
Bolin Heights Bldg. #1, CB# 3369
Chapel Hill, NC 27514-3369
Phone: (919) 966-2007
Fax: (919) 966-7080
E-mail: eb_registry@med.unc.edu
Website: http://www.med.unc.edu/derm/nebr_site

National Eye Institute
National Institutes of Health
31 Center Dr., Bldg. 31, Room 6A32, MSC 2510
Bethseda, MD 20892-2510
Phone: (301) 496-5248
E-mail: 2020@nei.nih.gov
Website: http://www.nei.nih.gov

National Familial Pancreas Tumor Registry
Johns Hopkins Hospital
Weinberg Building, Room 2242
401 North Broadway
Baltimore, MD 21231-2410
Phone: (410) 955-9132
Website: http://www.path.jhu.edu/pancreas

National Federation for the Blind
1800 Johnson Street
Baltimore, MD 21230
Phone: (410) 659-9314
E-mail: epc@roundley.com
Website: http://www.nfb.org

National Foundation for Depressive Illness, Inc.
PO Box 2257
New York, NY 10016
Phone: (212) 268-4260 or (800) 239-1265
Website: http://www.depression.org

National Foundation for Ectodermal Dysplasias
PO Box 114, 410 E Main
Mascoutah, IL 62258-0114
Phone: (618) 566-2020
Fax: (618) 566-4718
Website: http://www.nfed.org

National Foundation for Facial Reconstruction
317 East 34th Street #901
New York, NY 10016
Phone: (800) 422-3223
Website: http://www.nffr.org

National Foundation for Jewish Genetic Diseases, Inc.
250 Park Ave., Suite 1000
New York, NY 10017
Phone: (212) 371-1030
Website: http://www.nfjgd.org

National Foundation for the Blind
1800 Johnson Street
Baltimore, MD 21230
Phone: (410) 659-9314
Website: http://www.nfb.org

National Fragile X Foundation
PO Box 190488
San Francisco, CA 94119-0988
Phone: (800) 688-8765 or (510) 763-6030
Fax: (510) 763-6223
E-mail: natlfx@sprintmail.com
Website: http://nfxf.org

National Fragile X Syndrome Support Group
206 Sherman Road
Glenview, IL 60025
Phone: (708) 724-8626

National Gaucher Foundation
11140 Rockville Pike, Suite 350
Rockville, MD 20852-3106
Phone: (800) 925-8885
Website: http://www.gaucherdisease.org

National Heart, Lung, and Blood Institute
Two Rockledge Centre
6701 Rockledge Dr.
Bethesda, MD 20824-0105
Phone: (301) 592-8573
E-mail: nhlbiinfo@rover.nhlbi.nih.gov
Website: http://www.nhlbi.nih.gov

National Hemophilia Foundation
116 West 32nd Street, 11th Floor
New York, NY 10001
Phone: (800) 42-HANDI
Website: http://www.info@hemophilia.org

National Human Genome Research Institute
The National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
Phone: (301) 496-2433
Website: http://www.nhgri.nih.gov

National Hydrocephalus Foundation
12413 Centralia
Lakewood, CA 90715-1623
Phone: (562) 402-3523 or (888) 260-1789
E-mail: hydrobrat@earthlink.net
Website: http://www.nhfonline.org

National Incontinentia Pigmenti Foundation
30 East 72nd Street
New York, NY 10021
Phone: (212) 452-1231
Fax: (212) 452-1406
Website: http://imgen.bcm.tmc.edu/NIPF

National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
One AMS Circle
Bethesda, MD 20892
Website: http://www.nih.gov/niams

National Institute of Child Health and Human Development (NICHD)
Patient Recruitment and Public Liaison Office
Building 61, 10 Cloister Court
Bethesda, MD 20892-4754
Phone: (800) 411-1222
TTY: (301) 594-9774 or (866) 411-1010
E-mail: prpl@mail.cc.nih.gov
Website: http://clinicalstudies.info.nih.gov/detail/A_2000-CH-0141.html

National Institute of Diabetes and Digestive and Kidney Diseases
31 Center Dr., MSC 2560
Bethesda, MD 20892
Website: http://www.niddk.nih.gov

National Institute of Mental Health
6001 Executive Boulevard, Rm. 8184, MSC 9663
Bethesda, MD 20892-9663
Phone: (301) 443-4513
Fax: (301) 443-4279
Website: http://www.nimh.nih.gov/publicat/index.cfm

National Institute of Neurological Disorders and Stroke
31 Center Drive, MSC 2540, Bldg. 31, Room 8806
Bethesda, MD 20814
Phone: (301) 496-5751 or (800) 352-9424
Website: http://www.ninds.nih.gov

National Institute on Aging Information Center
PO Box 8057
Gaithersburg, MD 20898
Phone: (800) 222-2225 or (301) 496-1752

National Institute on Alcohol Abuse and Alcoholism
5600 Fishers Lane
Rockville, MD 20852

National Institute on Deafness and Other Communication Disorders
31 Center Dr., MSC 2320
Bethesda, MD 20814
Phone: (301) 402-0900
E-mail: nidcdinfo@nidcd.nih.gov
Website: http://www.nidcd.nih.gov

National Institutes of Health (NIH)
PO Box 5801
Bethesda, MD 20824
Phone: (800) 352-9424
Website: http://www.ninds.nih.gov/health

National Institutes of Health, Office of Rare Diseases
31 Center Dr., Bldg. 31, Room 1B-19, MSC 2084
Bethesda, MD 20892-2084
Phone: (301) 402-4336
Fax: (301) 480-9655
E-mail: hh70f@nih.gov
Website: http://rarediseases.info.nih.gov/ord

National Institutes of Health, Osteoporosis and Related Bone Diseases
National Resource Center
1232 22nd Street NW
Washington, DC 20037-1292
Phone: (202) 223-0344
Website: http://www.osteo.org/hypoph.html

National Kidney and Urologic Diseases Information Clearinghouse
3 Information Way
Bethesda, MD 20892-3560

National Kidney Foundation
30 East 33rd Street
New York, NY 10016
Phone: (800) 622-9010
Website: http://www.kidney.org

National Marfan Foundation
382 Main Street
Port Washington, NY 11050-3121
Phone: (800) 862-7326
Website: http://www.marfan.org

National MPS Society
102 Aspen Dr.
Downingtown, PA 19335
Phone: (610) 942-0100
Fax: (610) 942-7188
E-mail: info@mpssociety
Website: http://www.mpssociety.org

National Newborn Screening and Genetics Resource Center
1912 W. Anderson Lane, Suite 210
Austin, TX 78757
Phone: (512) 454-6419
Website: http://www.genes-r-us.uthscsa.edu

National Organization for Albinism and Hypopigmentation
1530 Locust Street #29
Philadelphia, PA 19102-4415
Phone: (215) 545-2322 or (800) 473-2310
Website: http://www.albinism.org

National Organization for Rare Disorders (NORD)
PO Box 8923
New Fairfield, CT 06812-8923
Phone: (203) 746-6518 or (800) 999-6673
Fax: (203) 746-6481
Website: http://www.rarediseases.org

National Organization of Mothers of Twins Clubs
PO Box 438
Thompson Station, TN 37179
Phone: (615) 595-0936
Website: http://www.nomotc.org

National Organization to Treat A-T
4316 Ramsey Ave.
Austin, TX 78756-3207
Phone: (877) TREAT-AT
Website: http://www. treat-at.org

National Registry for Ichthyosis and Related Disorders
University of Washington Dermatology Department
Box 356524, 1959 N.E. Pacific
Room BB1353
Seattle, WA 98195-6524
Phone: (800) 595-1265 or (206) 616-3179
Website: http://www.skinregistry.org

National Retinitis Pigmentosa Foundation
11350 McCormick Road, Executive Plaza 1, Suite 800
Hung Valley, MD 21031-1014
Phone: (800) 683-5555
Website: http://www.blindness.org

National Retinoblastoma Research and Support Foundation
PO Box 016880, 900 NW 17th Street, Room 257
Miami, FL 33101-6880
Phone: (800) 226-2734

National Sleep Foundation
1367 Connecticut Ave. NW, Suite 200
Washington, DC 20036
Phone: (202) 785-2300.

National Society of Genetic Counselors
233 Canterbury Dr.
Wallingford, PA 19086-6617
Phone: (610) 872-1192
Website: http://www.nsgc.org/GeneticCounselingYou.asp

National Society to Prevent Blindness
500 East Remington Road
Schaumburg, IL 60173
Phone: (708) 843-2020 or (800) 331-2020
Website: http://www.preventblindness.org

National Tay-Sachs and Allied Diseases Association
2001 Beacon Street, Suite 204
Brighton, MA 02135
Phone: (800) 906-8723
Fax: (617) 277-0134
E-mail: ntasd-Boston@worldnet.att.net
Website: http://www.ntsad.org

National Tourette Syndrome Association, Inc.
42-40 Bell Boulevard
Bayside, NY 11361-2820
Phone: (718) 224-2999
Fax: (718) 279-9596
E-mail: tourette@ix.netcom.com

National Urea Cycle Disorders Foundation
4841 Hill Street
La Canada, CA 91001
Phone: (800) 38-NUCDF
Website: http://www.NUCDF.org/

Nephrogenic Diabetes Insipidus Foundation
PO Box 1390
Eastsound, WA 98245
Phone: (888) 376-6343
Fax: (888) 376-3842
Website: http://www. Ndi.org

Neuropathy Association
60 E. 42nd Street Suite 942
New York, NY 10165
Phone: (212) 692-0662
Website: http://www.neuropathy.org

Nevus Network, The Congenital Nevus Support Group
PO Box 1981
Woodbridge, VA 22193
Phone: (703) 492-0253
Website: http://www.nevus.org

Nevus Outreach, Inc.
1616 Alpha Street
Lansing, MI 48910
Phone: (517) 487-2306
Website: http://www.nevus.org

Nofas
216 G Street NE
Washington, DC 20002
Phone: (202) 785-4585
Website: http://www.nofas.org

Norrie Disease Association
Massachusetts General Hospital E #6217, 149 13th Street
Charlestown, MA 02129
Phone: (617) 726-5718
E-mail: sims@helix.mgh.harvard.edu

O

Opitz G/BBB Family Network
PO Box 515
Grand Lake, CO 80447
E-mail: opitznet@mac.com
Website: http://www.gle.egsd.k12.co.us/opitz/index.html

Organic Acidemia Association
13210 35th Ave. North
Plymouth, MN 55441
Phone: (763) 559-1797
Fax: (763) 694-0017
Website: http://www.oaanews.org

Organic Acidemias UK
5 Saxon Road, Ashford
Middlesex, TW15 1QL
United Kingdom
Phone: (178) 424-5989

P

Pallister-Hall Foundation
RFD Box 3000, Fairground Road
Bradford, VT 05033

Pancreatitis Patients' Support Group
PO Box 164, Rochdale
Lancashire, OL11 5GY
United Kingdom
Website: http://www.zen.co.uk/home/page/ppsg/

Pancreatitis Support Network
Website: http://hometown.aol.com/karynwms/myhomepage/business.html

Parent Project for Muscular Dystrophy Research
1012 N. University Boulevard
Middletown, OH 45042
Phone: (413) 424-0696 or (800) 714-5437
E-mail: parentproject@aol.com
Website: http://www.parentdmd.org

Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS)
76 South New Boston
Francestown, NH 03043
Phone: (603) 547-8384
Website: http://www.smithmagenis.org

Parents of Galactosemic Children, Inc.
1100 West 49th Street
Austin, TX 78756-3199
Phone: (512) 458-7111
Website: http://www.tdh.state.tx.us/newborn/galac_1.htm

Pew Environmental Health Commission at the Johns Hopkins School of Public Health
111 Market Place, Suite 850
Baltimore, MD 21202
Phone: (410) 659-2690
Website: http://pewenvirohealth.jhsph.edu/html/reports/PEHCAsthmaReport.pdf

Pierre Robin Network
PO Box 3274
Quincy, IL 62305
Phone: (217) 224-7480
Website: http://www.pierrerobin.org/index.html

PMD Foundation
Contact: Mike Laprocido
Phone: (609) 636-2482
E-mail: mlaprocido@pmdfoundation.org
Website: http://www.pmdfoundation.org

Polycystic Kidney Disease Foundation
4901 Main Street
Kansas City, MO 64112-2634
Phone: (800) PKD-CURE
Website: http://www.pkdcure.org/home.htm

Polycystic Ovarian Syndrome Association
PO Box 80517
Portland, OR 97280
Phone: (877) 775-PCOS
Website: http://www.pcosupport.org

Prader-Willi Foundation
223 Main Street
Port Washington, NY 11050
Phone: (800) 253-7993
Website: http://www.prader-willi.org

Prader-Willi Syndrome Association
5700 Midnight Pass Road, Suite 6
Sarasota, FL 34242-3000
Phone: (941) 312-0400 or (800) 926-4797
Fax: (941) 312-0142
PWSAUSA@aol.com
Website: http://www.pwsausa.org

Prevent Blindness America
500 East Remington Road
Schaumburg, IL 60173
Phone: (800) 331-2020
Website: http://www.prevent-blindness.org

Proteus Syndrome Foundation
6235 Whetstone Dr.
Colorado Springs, CO 80918
Phone: (719)264-8445
E-mail: abscit@aol.com
Website: http://www.kumc.edu/gec/support/proteus.html

Pull-thru Network
316 Thomas Street
Bessemer, AL 35020
Phone: (205) 428-5953

R

Rainbows Down Under—A Trisomy 18 and Trisomy 13 Resource
SOFT Australia, 198 Oak Road
Kirrawee, NSW 2232
Australia

Phone: 02-9521-6039
Website: http://members.optushome.com.au/karens

Raynaud's & Scleroderma Association (UK)
112 Crewe Road, Alsager
Cheshire, ST7 2JA
United Kingdom
Phone: (44) (0) 1270 872776
E-mail: webmaster@raynauds.demon.co.uk
Website: http://www.raynauds.demon.co.uk

Research Registry for Hereditary Hearing Loss
555 N. 30th Street
Omaha, NE 68131
Phone: (800) 320-1171
Website: http://www.boystown.org/btnrh/deafgene.reg/waardsx.htm

RESOLVE, The National Infertility Association
1310 Broadway
Somerville, MA 02144-1779
Phone: (617) 623-0744
E-mail: resolveinc@aol.com
Website: http://www.resolve.org

Retina International
Ausstellungsstrasse 36
Zürich, CH-8005
Switzerland
Phone: (+41 1 444 10 77)
Website: http://www.retina-international.org

Retinitis Pigmentosa International
23241 Ventura Boulevard, Suite 117
Woodland Hills, CA 91364
Phone: (818) 992-0500 or (800) 344-4877
E-mail: rpint@pacbell.net
Website: http://www.rpinternational.org

Rett Syndrome Research Foundation
4600 Devitt Dr.
Cincinnati, OH 45246
Website: http://www.rsfr.org

Rhizomelic Chondrodysplasia Punctata (RCP) Family Support Group
137 25th Ave.
Monroe, WI 53566

Robinow Syndrome Foundation
PO Box 1072
Anoka, MN 55303
Phone: (612) 434-1152
Website: http://www.robinow.org

Royal National Institute for the Blind
PO Box 173
Peterborough, PE2 6WS
United Kingdom
Website: http://www.rnib.uk

Rubinstein-Taybi Parent Support Group
Attn: Lorrie Baxter
PO Box 146
Smith Center, KS 66967
Phone: (888) 447-2989
E-mail: lbaxter@ruraltelnet
Website: http://www.specialfriends.org

Russell-Silver Syndrome Support Group: Yahoo Groups
Website: http://groups.yahoo.com/group/RSS-Support

S

SADS Foundation
PO Box 58767, 508 East South Temple, Suite 20
Salt Lake City, UT 84102
Phone: (800) 786-7723
Website: http://www.sads.org

Schepens Eye Research Institute
20 Staniford Street
Boston, MA 02114-2500
Phone: (617) 912-0100
Website: http://www.eri.harvard.edu

Schizophrenics Anonymous
15920 W. Twelve Mile
Southfield, MI 48076
Phone: (248) 477-1983

Scleroderma Foundation
12 Kent Way, Suite 101
Byfield, MA 01922
Phone: (978) 463-5843 or (800) 722-HOPE
Fax: (978) 463-5809
Website: http://www.scleroderma.org

SHARE—Pregnancy and Infant Loss Support, Inc.
St Joseph Health Center
300 First Capital Dr.
St. Charles, MO 63301
Phone: (800) 821-6819

Short Stature Foundation
4521 Campus Drive, #310
Irvine, CA 92715
Phone: (714) 559-7131 or (800) 243-9273

Shriners Hospitals for Children
International Shrine Headquarters
2900 Rocky Point Dr.
Tampa, FL 33607-1460
Phone: (813) 281-0300

Skin Cancer Foundation
245 Fifth Ave., Suite 1403
New York, NY 10016
Phone: (800) 754-6490
E-mail: info@skincancer

Smith-Lemli-Opitz Advocacy and Exchange (RSH/SLO)
2650 Valley Forge Dr.
Boothwyn, PA 19061
Phone: (610) 485-9663
Website: http://members.aol.com/slo97/index.html

Society for Mucopolysaccharide Diseases
46 Woodside Road, Amersham
Buckinghamshire, HP6 6AJ
United Kingdom
Phone: +44 (01494) 434156
Website: http://www.mpssociety.co.uk

Sotos Syndrome Support Group
Three Danda Square East #235
Wheaton, IL 60187
Phone: (888) 246-SSSA or (708) 682-8815
Website: http://www.well.com/user/sssa/

Spina Bifida Association of America
4590 MacArthur Boulevard NW
Suite 250
Washington, DC 20007-4226
Phone: (800) 621-3141 or (202) 944-3285
Fax: (202) 944-3295

SRPS Family Network (Short Rib Polydactly Syndrome)
Website: http://www.srps.net

Stanford Center for Narcolepsy
1201 Welch Rd., Room P-112
Stanford, CA 94305
Phone: (415) 725-6517

Stickler Involved People
15 Angelina
Augusta, KS 67010
Phone: (316) 775-2993
Website: http://www.sticklers.org/sip

Sudden Arrhythmia Death Syndrome Foundation
PO Box 58767
508 East South Temple, Suite 20
Salt Lake City, UT 84102
Phone: (800) 786-7723
E-mail: sads@sads
Website: http://www.sads.org

Sudden Infant Death Syndrome Network
PO Box 520
Ledyard, CT 06339
Website: http://sids-network.org

Support for Parents with Hypospadias Boys
Website: http://clubs.yahoo.com/clubs/mumswithhypospadiaskids

Support Groups For MMA Organic Acidemia Association
13210 35th Ave
Plymouth, MN 55441
Phone: (763) 559-1797
Website: http://www.oaanews.org

Support Organization for Trisomy 18, 13, and Related Disorders (SOFT)
2982 South Union Street
Rochester, NY 14624
Phone: (800) 716-SOFT
Website: http://www.trisomy.org

T

T.A.R.S.A. Thrombocytopenia Abset Radius Syndrome Association
212 Sherwood Dr.
Linwood, NJ 08324-7658
Phone: (609) 927-0418

Task Force on Xeroderma Pigmentosum
American Academy of Dermatology
Box 4014
Schaumburg, IL 60168-4014
Phone: (708) 330-0230

Texas Heart Institute Heart Information Service
PO Box 20345
Houston, TX 77225-0345
Phone: (800) 292-2221
Website: http://www.tmc.edu/thi/his.html

Tourette Syndrome Foundation of Canada
194 Jarvis Street, #206
Toronto, ON M5B 2B7
Canada
Phone: (800) 361-3120
E-mail: tsfc.org@sympatico.ca
Website: http://www.tourette.ca

Treacher Collins Foundation
Box 683
Norwich, VT 05055
Phone: (800) 823-2055

Triple X Syndrome Support
231 W. Park Ave.
Sellersville, PA 18960
Phone: (215) 453-2117
E-mail: edr@starbyte.com
Website: http://www.voicenet.com/~markr/triple.html

Tuberous Sclerosis Alliance
801 Roeder Road, Suite 750
Silver Spring, MD 20910
Phone: (800) 225-6872
Website: http://www.tsalliance.org

Turner Syndrome Society of Canada
7777 Keele St, Floor 2
Concord, ON L4K 1Y7
Canada
Phone: (800) 465-6744 or (416) 660-7766
Fax: (416) 660-7450

Turner Syndrome Society of England
2 Mayfield Ave.
London, W41PW
England
Phone: 44 (0)181-994 7625
Fax: 44 (0)181-995 9075
Website: http://www.tss.org.uk

Turner Syndrome Society of the United States
14450 T. C. Jester, Suite 260
Houston, TX 77014
Phone: (800) 365-9944 or (832) 249-9988
Fax: (832) 249-9987
E-mail: tesch@turner-syndrome-us.
Website: http://www.turner-syndrome-us.org

Twin Hope, Inc.
2592 West 14th Street
Cleveland, OH 44113
Phone: (502) 243-2110
Website: http://www.twinhope.com

Twins Foundation
PO Box 6043
Providence, RI 02940-6043
Phone: (401) 751-8946
E-mail: Twins@twinsfoundation.com

U

U.S. National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

United Cerebral Palsy Association, Inc. (UCP)
1660 L Street NW, Suite 700
Washington, DC 20036-5602
Phone: (202)776-0406 or (800)872-5827
Website: http://www.ucpa.org

United Leukodystrophy Foundation
2304 Highland Dr.
Sycamore, IL 60178
Phone: (815) 895-3211 or (800) 728-5483
Fax: (815) 895-2432
Website: http://www.ulf.org

United Mitochondrial Disease Foundation
PO Box 1151
Monroeville, PA 15146-1151
Phone: (412) 793-8077
Fax: (412) 793-6477
Website: http://www.umdf.org

University of California Center for the Study and Treatment of Hypospadias
University of California Medical Center
400 Parnassus, Room A-610
San Francisco, CA 94143-0330
Phone: (415) 353-2200
Fax: (415) 353-2480
E-mail: lbaskin@urol.ucsf.edu
Website: http://itsa.ucsf.edu/~uroweb/Uro/hypospadias/index.html

University of Illinois Center for Narcolepsy Research
845 S. Damen Ave.
Chicago, IL 60612
Phone: (312) 996-5176

University of Pennsylvania Cancer Center
3400 Spruce Street
Philadelphia, PN 19104
Phone: (215) 662-4000
Website: http://www.oncolink.upenn.edu

University of Texas M. D. Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030
Phone: (800) 392-1611
Website: http://www.mdanderson.org

Usher Family Support
4918 42nd Ave. South
Minneapolis, MN 55417
Phone: (612) 724-6982

V

VACTRLS Association Family Network
5585 CY Ave

Casper, WY 82604
Website: http://www.homestead.com/VAFN/VAFN.html

VATER Connection
1722 Yucca Lane
Emporia, KS 66801
Phone: (316) 342-6954
Website: http://www.vaterconnection.org

Velo-Cardio-Facial Syndrome Educational Foundation
Upstate Medical University Hospital
708 Jacobsen Hall (C.D.U.)
750 East Adams Street
Syracuse, NY 13210

Velo-Cardio-Facial Syndrome Research Institute
Albert Einstein College of Medicine
3311 Bainbridge Ave.
Bronx, NY 10467
Phone: (718) 430-2568
Fax: (718) 430-8778
E-mail: rgoldber@aecom.yu.edu
Website: http://www.kumc.edu/gec/vcfhome.html

Vestibular Disorders Association
PO Box 4467
Portland, OR 97208-4467
Phone: (800) 837-8428
Website: http://www.vestibular.org

VHL Family Alliance
171 Clinton Ave.
Brookline, MA 02455-5815
Phone: (800) 767-4VHL
Website: http://www.vhl.org

Vision Community Services
23 A Elm Street
Watertown, MA 02472
Phone: (617) 926-4232 or (800) 852-3029
Website: http://www.mablind.org

W

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 E. 84th Street
New York, NY 10024
Phone: (212) 875-8312 or (800) 437-MOV2
Fax: (212) 875-8389
E-mail: wemove@wemove
Website: http://www.wemove.org

Weaver Syndrome Families Support (WSFS)
4357 153rd Ave. SE
Bellevue, WA 98006
Phone: (425) 747-5382

WideSmiles
PO Box 5153
Stockton, CA 95205-0153
Phone: (209) 942-2812
Website: http://www.widesmiles.org

Williams Syndrome Association
1312 N. Campbell, Suite 34
Royal Oak, MI 48067
Phone: (248) 541-3630
Fax: (248) 541-3631

Williams Syndrome Foundation
University of California
Irvine, CA 92679-2310
Phone: (949) 824-7259
Website: http://wsf.org

Wilson's Disease Association
4 Navaho Dr.
Brookfield, CT 06804
Phone: (800) 399-0266

World Arnold-Chiari Malformation Association
31 Newton Woods Road
Newton Square
Philadelphia, PA 19073
Website: http://presenter.com?~wacma/milhorat.htm

World Craniofacial Foundation
PO Box 515838
7777 Forest Lane, Suite C-621
Dallas, TX 75251-5838
Phone: (972) 566-6669 or (800) 533-3315
E-mail: worldcf@worldnet.att.net
Website: http://www.worldcf.org

X

Xeroderma Pigmentosum Registry
New Jersey Medical School
Department of Pathology
185 South Orange Ave., Room C-520
Newark, NJ 07103-2714
Phone: (201) 982-4405

Xeroderma Pigmentosum Society, Inc.
PO Box 4759
Poughkeepsie, NY 12602
Phone: (518) 851-2612
E-mail: xps@xps
Website: http://www.xps.org

Y

Yale-LDA Social Learning Disabilities Project
Yale Child Study Center
230 South Frontage Road
New Haven, CT 06520-7900
Phone: (203) 785-3488
Website: http://info.med.Yale.edu/chldstdy/autism

Z

Zain Hansen MPS Foundation
23400 Henderson Road
Covelo, CA 95420
Phone: (800) 767-3121

GLOSSARY

A

5′ VNTR A specific variation outside the insulin gene that is implicated in NIDDM and IDDM susceptibility.

AADC INHIBITORS Drugs that block the amino acid decarboxylase; one type of enzyme that breaks down dopamine. Also called DC inhibitors, they include carbidopa and benserazide.

ABDOMINAL HERNIA Bulging of an organ or tissue through the muscle of the stomach wall.

ABDUCENS NERVE Cranial nerve VI; the nerve that extends from the midbrain to the lateral rectus muscle of the eye and controls movement of the eye toward the ear (abduction).

ABDUCTION Turning away from the body.

ABSCESS A localized collection of pus or infection that is walled off from the rest of the body.

ABSENCE SEIZURE A brief seizure with an accompanying loss of awareness or alertness.

ACAMPROSATE An anti-craving medication used in Europe to reduce the craving for alcohol. It is presently undergoing tests for approval in the United States.

ACANTHOCYTOSIS The presence of acanthocytes in the blood. Acanthocytes are red blood cells that have the appearance of thorns on their outer surface.

ACANTHOSIS NIGRICANS A skin condition characterized by darkly pigmented areas of velvety wart-like growths. Acanthosis nigricans usually affects the skin of the armpits, neck, and groin.

ACCOMMODATION The ability of the lens to change its focus from distant to near objects. It is achieved through the action of the ciliary muscles that change the shape of the lens.

ACETYLCHOLINESTERASE (ACHE) An enzyme found in nerve tissue.

ACHROMATOPSIA The inability to distinguish any colors.

ACID MALTASE The enzyme that regulates the amount of glycogen stored in muscle cells. When too much glycogen is present, acid maltase is released to break it down into waste products.

ACIDOSIS A condition of decreased alkalinity resulting from abnormally high acid levels (low pH) in the blood and tissues. Usually indicated by sickly sweet breath, headaches, nausea, vomiting, and visual impairments.

ACONDROPLASIA An autosomal dominant form of dwarfism caused by a disorder in the formation of cartilage at the ends of long bones. Affected individuals typically have short limbs, a large head with a prominent forehead and flattened profile, and a normal-sized trunk.

ACQUIRED ANGIONEUROTICEDEMA Abbreviated AANE, or AAE, this is a non-hereditary form of angio edema that generally begins to show symptoms in, or after, the fourth decade of life.

ACQUIRED IMMUNITY Also called ‘specific immunity;’ refers to immune reaction mediated by B-cells and/or T-cells. Includes humoral and cellular immunity.

ACROCENTRIC A chromosome with the centromere positioned at the top end.

ACROCEPHALOPOLYSYNDACTYLY SYNDROMES A collection of genetic disorders characterized by cone shaped abnormality of the skull and partial fusing of adjacent fingers or toes.

ACROCEPHALY An abnormal cone shape of the head.

ACROMELIC The anatomical term used to denote the end of a limb (arm or leg). In the context of Robinow syndrome, it refers to bones of the hands and feet.

ACROOSTEOLYSIS Loss of bone tissue at the ends of the fingers and/or toes.

ACROPARESTHESIAS Painful burning sensation in hands and feet.

ACTION POTENTIAL The wave-like change in the electrical properties of a cell membrane, resulting from the difference in electrical charge between the inside and outside of the membrane.

ACUTE PHASE The initial phase of LHON where visual blurring begins in both eyes and central vision is lost.

ACUTE PHASE REACTANTS Blood proteins whose concentrations increase or decrease in reaction to the inflammation process.

ADDUCTED THUMBS Thumbs clasped across the palm.

ADDUCTION Movement toward the body. In Duane retraction syndrome, turning the eye inward toward the nose.

ADENOCARCINOMA A type of cancer that is in a gland-like form.

ADENOMATOUS Derived from glandular structures.

ADRENAL GLAND A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

ADRENAL INSUFFICIENCY Problems with the adrenal glands that can be life threatening if not treated. Symptoms include sluggishness, weakness, weight loss, vomiting, darkening of the skin and mental changes.

ADRENOCORTICOTROPIN (CORTICOTROPHIN) A hormone that acts on cells of the adrenal cortex, causing them to produce male sex hormones and hormones that control water and mineral balance in the body.

ADVANCED BONE AGE The bones, on x ray, appear to be those of an older individual.

AFFECTIVE FLATTENING A loss or lack of emotional expressiveness. It is sometimes called blunted or restricted affect.

AFLATOXIN A substance produced by molds that grow on rice and peanuts. Exposure to aflatoxin is thought to explain the high rates of primary liver cancer in Africa and parts of Asia.

AGE-ASSOCIATED MEMORY IMPAIRMENT (AAMI) A condition in which an older person experiences some memory loss and takes longer to learn new information. AAMI is distinguished from dementia in that it is not progressive and does not represent a serious decline from the person's previous level of functioning.

AGENESIS Failure of an organ, tissue, or cell to develop or grow.

AGENESIS OF THE CORPUS CALLOSUM Failure of the corpus callosum to form and develop. The corpus callosum is the band of nerve fibers located between the two sides, or hemispheres, of the brain.

AGNOSIA Loss of the ability to recognize objects by use of the physical senses.

AGYRI A lack of convolutions (gyri) or normal folds in the brain tissue.

AKATHISIA Agitated or restless movement, usually affecting the legs and accompanied by a sense of discomfort. It is a common side effect of neuroleptic medications.

AKINESIA A loss of the ability to move; freezing in place.

ALKALINE Having a basic pH; not acidic.

ALKALINIZATION The process of making a solution more basic, rather than more acidic, by raising the pH.

ALLELE One of two or more alternate forms of a gene.

ALLELIC Related to the same gene.

ALLELIC VARIANTS A disease is said to have allelic variants when different mutations in the same allele result in identical, or nearly identical, symptoms. An allele is the combined locations of a gene on the two paired chromosomes that contain this gene.

ALLERGEN A substance or organism foreign to the body. Allergens stimulate the immune system to produce antibodies.

ALLERGIC RHINITIS Hay fever.

ALLERGY Condition in which the immune system is hypersensitive to contact with allergens; an abnormal response by the immune system to contact with an allergen. This condition produces symptoms such as inflammation of tissues and production of excess mucus in the respiratory system.

ALOPECIA Loss of hair or baldness.

ALOPECIA AREATA A nonscarring hair loss syndrome characterized by smooth round or oval hairless areas on the scalp.

ALPHA-FETOPROTEIN (AFP) A chemical substance produced by the fetus and found in the fetal circulation.

AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

ALPHA-L-IDURONIDASE. An enzyme that breaks down dermatan sulfate and heparan sulfate. People with Hurler syndrome do not make enough of this enzyme.

ALPHA-THALASSEMIA Autosomal recessive disorder where no functional hemoglobin is produced. Leads to severe untreatable anemia.

ALTERATION Change or mutation in a gene, specifically in the DNA that codes for the gene.

ALTERNATE COMPLEMENT PATHWAY A cascade of enzymatic reactions that produce antibacterial proteins. This pathway helps to ward off infections.

ALZHEIMER DISEASE A degenerative disease of the central nervous system characterized by premature senility and other mental deterioration.

AMASTIA A birth disorder involving absent breast(s).

AMELOGENESIS IMPERFECTA A hereditary dental abnormality characterized by discoloration of the teeth.

AMINO ACID Organic compounds that form the building blocks of protein. There are 20 amino acids (eight are "essential amino acids" that the body cannot make and must be obtained from food).

AMNIOCENTESIS A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

AMNION Thin, tough membrane surrounding the embryo and containing the amniotic fluid.

AMNIOTIC FLUID The fluid surrounding a developing baby during pregnancy.

AMNIOTIC SAC Contains the fetus and its surrounding amniotic fluid.

AMPLIFICATION A process by which something is made larger. In clotting, only a very few chemicals are released by the initial injury; they result in a cascade of chemical reactions which produces increasingly larger quantities of different chemicals, resulting in an appropriately-sized, strong fibrin clot.

AMPUTATION Surgical removal of any portion of the body.

AMYLASE A digestive enzyme found in saliva or pancreatic fluid that breaks down starch and sugars.

AMYLOID A waxy translucent substance composed mostly of protein, that forms plaques (abnormal deposits) in the brain.

AMYLOIDOSIS Accumulation of amyloid deposits in various organs and tissues in the body such that normal functioning of an organ is compromised.

AMYOPLASIA The mildest form of arthrogryposis muliplex congenita, characterized by sporadic and recurrent contractures of the wrists, elbows, and knees; clubfoot, and an abnormal internal rotation of the shoulders.

ANAGEN The growth phase of the human hair growth cycle.

ANALYTE A chemical substance such as an enzyme, hormone, or protein.

ANDROGENS A group of steroid hormones that stimulate the development of male sex organs and male secondary sexual characteristics.

ANEMIA A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

ANESTHESIA Lack of normal sensation (especially to pain) brought on by medications just prior to surgery or other medical procedures.

ANESTHETIC Drug used to temporarily cause loss of sensation in an area of the body. An anesthetic may either be general, associated with a loss of consciousness, or local, affecting one area only without loss of consciousness. Anesthetics are administered either via inhalation or needle injection.

ANEUPLOIDY An abnormal number of chromosomes in a cell. Trisomy 18 and trisomy 13 are examples of aneuploid conditions.

ANEURYSM Widening of an artery, which could eventually bleed.

ANGELMAN SYNDROME A syndrome caused by a deletion in the maternally inherited chromosome 15 or uniparental disomy of the paternal chromsome 15.

ANGIOGRAPHY Injecting dye into blood vessels so they can be be seen on a radiograph or picture.

ANGIOID STREAKS Gray, orange, or red wavy branching lines in Bruch's membrane.

ANGIOKERATOMA Skin rash comprised of red bumps. The rash most commonly occurs between the belly button and the knees.

ANGIOMA A benign tumor composed of blood vessels or lymph vessels.

ANGIONEUROTIC EDEMA Recurrent episodes of swelling of the tissues of the body caused by an overactive immune system. This is also called angioedema.

ANGIOTENSINOGEN A plasma globulin (protein) formed in the liver and directly involved in the regulation of blood pressure.

ANKYLOSIS Immobility of a joint due to the formation of new bone at the site of inflammation.

ANOMALOUS Irregular or different from normal.

ANOMALOUS VENOUS RETURN Normally, the veins that bring blood containing oxygen from the lungs to the heart (called pulmonary veins) are connected to the left atrium. In this situation, the pulmonary veins are connected to the right atrium.

ANOMALY Different from the normal or expected. Unusual or irregular structure.

ANOPTHALMIA A medical condition in which one eye is missing.

ANOTIA Absence of an ear.

ANTERIOR FONTANELLE The soft-spot on the skull of an infant that is located in the center of the head just behind the hairline.

ANTERIOR HORN CELLS Subset of motor neurons within the spinal cord.

ANTI-ANDROGEN DRUGS Drugs that block the activity of the male hormone.

ANTIBIOTICS A group of medications that kill or slow the growth of bacteria.

ANTIBODY A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

ANTICIPATION Increasing severity in disease with earlier ages of onset in successive generations; a condition that begins at a younger age and is more severe with each generation.

ANTICOAGULANT Drugs used to prevent blood clots.

ANTIDIURETIC HORMONE (VASOPRESSIN) A hormone that acts on the kidneys to regulate water balance.

ANTIGEN A substance or organism that is foreign to the body and stimulates a response from the immune system.

ANTIGEN PRESENTING CELL Cells that are able to present foreign antigen in conjunction with major histocompatability complex proteins to the immune system.

ANUS The opening at the end of the intestine that carries waste out of the body.

AORTA The main artery located above the heart that pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

AORTIC REGURGITATION A condition in which the aortic valve does not close tightly, allowing blood to flow backwards from the aorta into the heart.

AORTIC ROOT The location where the aorta (main heart blood vessel) inserts in the heart. Enlargement of the aortic root can cause it to rupture.

AORTIC STENOSIS A condition in which the aortic valve does not open properly, making it difficult for blood to leave the heart.

APHASIA Loss of previously acquired ability to speak, or to understand written or spoken language.

APLASTIC ANEMIA A form of anemia characterized by a greatly decreased formation of red and white blood cells as a result of abnormal bone marrow.

APNEA An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

APOENZYME An enzyme that cannot function without assistance from other chemicals called cofactors.

APOPTOSIS The normally programmed cell death process in which cells die in order to be replaced with new cells.

APPENDECTOMY The procedure to surgically remove an appendix.

APPENDICITIS Inflammation of the appendix.

APPENDIX A portion of intestine attached to the cecum.

APRAXIA Impairment of the ability to make purposeful movements, but not paralysis or loss of sensation.

AQUEOUS HUMOR A fluid produced by the ciliary body and contained within the front chamber of the eye.

ARACHNODACTYLY A condition characterized by abnormally long and slender fingers and toes.

ARRHYTHMIA Abnormal heart rhythm. Examples are a slow, fast, or irregular heart rate.

ARTERIOLE The smallest type of artery.

ARTERIOPATHY Damage to blood vessels.

ARTERIOSCLEROSIS Hardening of the arteries that often results in decreased ability of blood to flow smoothly.

ARTERIOVENOUS MALFORMATION (AVM) Abnormal, direct connection between the arteries and veins (blood vessels). Can range from very small to large in size. Bleeding or an aneurysm may result.

ARTERY A blood vessel that carries blood away from the heart to peripheral tissues.

ARTHROCHALASIA Excessive loosness of the joints.

ARTHROGRYPOSIS Abnormal joint contracture.

ASPERGER SYNDROME A term used to describe high-functioning individuals with autism. These individuals usually have normal IQ and some language skills.

ASPHYXIA Lack of oxygen. In the case of cerebral palsy, lack of oxygen to the brain.

ASPIRATION Inhalation of food or saliva.

ASPIRATION PNEUMONIA Lung infection due to food or liquids accidentally getting into lungs.

ASPLENIA The absence of the spleen in the body.

ASTIGMATISM A cause of poor eyesight, usually due to an error in the refraction of light within the eye.

ASTROCYTOMA Tumor of the central nervous system derived from astrocytes.

ASYMMETRIC SEPTAL HYPERTROPHY A condition in which the septum (the wall that separates the atria of the heart) is abnormally excessively thickened. In microscopic examination, normal alignment of muscle cells is absent (myocardial disarray).

ASYMPTOMATIC CARRIER A person who carries a recessive trait but does not show any characteristics of the trait.

ATAXIA A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

ATHEROSCLEROSIS Hardening of the arteries caused by cholesterol and fat deposits. Increases risk of heart disease, stroke, and other complications.

ATHETOSIS A condition marked by slow, writhing, involuntary muscle movements.

ATOPIC A condition or disease that is the result of an allergic reaction.

ATOPIC ASTHMA Asthma caused by an allergic reaction; atopic asthma tends to have a strong inherited component (tends to run in families).

ATOPIC RHINITIS Also referred to as "hay fever;" symptoms of rhinitis caused by an allergic response to the presence of an allergen (such as tree or grass pollen).

ATP Adenosine triphosphate. The chemical used by the cells of the body for energy.

ATRESIA An abnormal condition in which a structure that should be hollow is fused shut.

ATRIA/ATRIUM The upper chamber of the heart. Typically, there are two atrias, one on the right side and one on the left side of the heart.

ATRIAL SEPTAL DEFECT An opening between the right and left atria of the heart.

ATROPHIC DERMATOSIS Wasting away of the skin.

ATROPHIC PHASE The final phase of LHON where cells in the optic disc and optic nerve have atrophied, resulting in legal blindness. Peripheral vision remains.

ATROPHY Wasting away of normal tissue or an organ due to degeneration of the cells.

ATTENTION DEFICIT DISORDER (ADD) Disorder characterized by a short attention span, impulsivity, and in some cases hyperactivity.

ATYPIA Lacking uniformity.

ATYPICAL PERSONALITY DEVELOPMENT Another term for pervasive development disorder (PDD-NOS). Other synonyms for this diagnostic category are atypical autism and atypical PDD.

AUDIOGRAM A graph of hearing level versus frequency. An audiologist plots the hearing loss of a patient on this graph to help determine the type of hearing loss and possible treatments.

AUDITORY NERVE The nerve responsible for transmitting electrical impulses created within the ear in response to sounds to the brain.

AURICULO Related to the ear.

AUTISM A syndrome characterized by a lack of responsiveness to other people or outside stimulus. Often in conjunction with a severe impairment of verbal and non-verbal communication skills.

AUTISTIC PSYCHOPATHY Hans Asperger's original name for Asperger syndrome. It is still used occasionally as a synonym for the disorder.

AUTISTIC SPECTRUM DISORDERS Another term for the pervasive developmental disorders.

AUTOANTIBODY An antibody that reacts against part of the self.

AUTOIMMUNE Referring to an immune reaction erroneously directed toward 'self' tissues.

AUTOIMMUNE DISEASE Describes a group of diseases characterized by an inflammatory immune reaction erroneously directed toward 'self' tissues.

AUTOIMMUNE DISORDER A disorder in which the body's immune cells mistake the body's own tissues as foreign invaders; the immune cells then work to destroy tissues in the body.

AUTONOMIC NERVOUS SYSTEM The part of the nervous system that regulates heart muscle, smooth muscle, and glands.

AUTOSOMAL Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

AUTOSOMAL DISEASE A disease caused by a gene located on an autosomal chromosome.

AUTOSOMAL DOMINANT A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

AUTOSOMAL DOMINANT MUTATION An abnormal gene on one of the 22 pairs of non-sex chromosomes that will display the disorder when only one copy is inherited.

AUTOSOMAL RECESSIVE A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

AUTOSOMAL RECESSIVE MUTATION A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

AUTOSOME Chromosome not involved in specifying sex.

AXON Skinny, wire-like extension of nerve cells.

B

B CELL Specialized type of white blood cell that is capable of secreting infection-fighting antibodies.

BALANCED CHROMOSOME TRANSLOCATION A rearrangement of the chromosomes in which two chromosomes have broken and exchanged pieces without the loss of genetic material.

BAND A specific region of a chromosome that is identified by its characteristic staining pattern and location within a chromosome, as seen in a karyotype. A band is either part of the short arm (p arm) or the long arm (q arm) of a chromosome and is further defined by a numeric location, such as chromosome band 11q24.1.

BARIUM A chemical put into a solution and swallowed to help with outlining the gastrointestinal system during an x-ray study.

BARIUM ENEMA X RAY A procedure that involves the administration of barium into the intestines by a tube inserted into the rectum. Barium is a chalky substance that enhances the visualization of the gastrointestinal tract on x ray.

BASAL GANGLIA A section of the brain responsible for smooth muscle movement.

BASE PAIRS Building blocks of DNA, the chemical that genes are made of.

BASEMENT MEMBRANE Part of the epithelium, or outer layer of the cornea.

BECKER MUSCULAR DYSTROPHY (BMD) A type of muscular dystrophy that affects older boys and men, and usually follows a milder course than Duchenne muscular dystrophy.

BECKWITH-WIEDEMANN SYNDROME A collection of health problems present at birth including an omphalocele, large tongue, and large body size.

BENIGN A non-cancerous tumor that does not spread and is not life-threatening.

BENIGN PROSTATIC HYPERPLASIA (BPH) A non-cancerous condition of the prostate that causes growth of the prostate tissue, thus enlarging the prostate and blocking urination.

BENIGN TUMOR An abnormal proliferation of cells that does not spread to other sites.

BENZOQUINONE ACETIC ACID Toxic compound that is formed when oxygen reacts with homogentisic acid.

BETA CELLS Specialized cells of the pancreas that make insulin.

BETA-2 MICROGLOBULIN A component protein of class I MHC (major histocompatibility complex).

BETA-ADRENERGIC BLOCKER A drug that works by controlling the nerve impulses along specific nerve pathways.

BILATERAL Relating to or affecting both sides of the body or both of a pair of organs.

BILATERAL BREAST CANCER Cancer of both breasts, caused by two separate cancer processes.

BILE A substance produced by the liver, and concentrated and stored in the gallbladder. Bile contains a number of different substances, including bile salts, cholesterol, and bilirubin.

BILE ACIDS Steroid acids such as cholic acid that occur in bile, an alkaline fluid secreted by the liver and passed into a part of the small intestine where it aids in absorption of fats.

BILE ALCOHOL A steroid acid with an alcohol group attached.

BILE DUCT A passageway that carries bile (fluid secreted by the liver involved in fat absorption) from the liver to the gallbladder to the small intestine.

BILIRUBIN A yellow pigment that is the end result of hemoglobin breakdown. This pigment is metabolized in the liver and excreted from the body through the bile. Bloodstream levels are normally low; however, extensive red cell destruction leads to excessive bilirubin formation and jaundice.

BIOCHEMICAL TESTING Measuring the amount or activity of a particular enzyme or protein in a sample of blood, urine, or other tissue from the body.

BIOPSY The surgical removal and microscopic examination of living tissue for diagnostic purposes.

BIOPTICS Glasses that have small telescopes fitted in the lens.

BIOSYNTHESIS The manufacture of materials in a biological system.

BIOTIN A growth vitamin of the vitamin B complex found naturally in liver, egg yolks, and yeast.

BIPOLAR DISORDER Formerly called "manic depression," this psychological disorder is characterized by periods of mania followed by periods of depression.

BITEMPORAL CONSTRICTION Abnormal narrowing of both sides of the forehead.

BLACKFAN-DIAMOND SYNDROME (BDS) A disorder with congenital hypoplastic anemia. Some researchers believe that some or all individuals with Aase syndrome actually have BDS; that Aase syndrome and BDS are not separate disorders.

BLADDER The organ that stores urine after it flows out of the kidneys and through the ureters.

BLEPHAROPHIMOSIS A small eye opening without fusion of the upper eyelid with the lower eyelid at the inner and outer corner of the eye.

BLEPHAROSPASM A focal dystonia marked by excessive blinking and involuntary closing of the eyes.

BLOOD VESSELS General term for arteries, veins, and capillaries that transport blood throughout the body.

BODY ASYMMETRY Abnormal development of the body in which the trunk and/or the limbs are not of equal size from one side of the body to the other.

BONE MARROW A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

BONE MARROW TRANSPLANT (BMT) A medical procedure used to treat some diseases that arise from abnormal blood cell formation in the bone marrow. Healthy bone marrow is extracted from a donor to replace the marrow in an ailing individual. Proteins on the surface of bone marrow cells must be identical or very closely matched between a donor and the recipient.

BOWMAN'S LAYER Transparent sheet of tissue directly below the basement membrane.

BOY IN THE BUBBLE A description for SCID since these children need to be isolated from exposure to germs, until they are treated by bone marrow transplantation or other therapy.

BRACHYCEPHALY An abnormal thickening and widening of the skull.

BRACHYDACTYLY Abnormal shortness of the fingers and toes.

BRACHYMELIA A general medical term used to describe short limbs.

BRADYKINESIA Extremely slow movement.

BRAILLE An alphabet represented by patterns of raised dots that can be felt with the fingertips. It is the main method of reading used by the blind today.

BRAIN VENTRICLES A set of four connected cavities that are located deep in the core of the brain. Cerebrospinal fluid is made by cells lining the walls of the first two ventricles, then flows through the third, then fourth ventricle before flowing out of the brain. The fluid-filled cavities provide mechanical cushion for the brain, and the CSF provides nutrients to, and carries metabolic wastes away from, the cells of the brain.

BRANCHED-CHAIN An open chain of atoms having one or more side chains.

BRCA2 Gene, when altered, known to cause increased risks of breast, ovarian, and, possibly pancreatic cancer.

BREAST BIOPSY Small sample of tissue taken from the breast and studied to diagnose and determine the exact type of breast cancer.

BREAST SELF-EXAM (BSE) Examination by an individual of their own breasts.

BREECH DELIVERY Birth of an infant feet or buttocks first.

BROAD LIGAMENT The ligament connecting the ovaries to the uterus.

BRONCHI Branching tube-like structures that carry air in and out of the lungs. Walls of bronchi contain circular muscles that can constrict (tighten up to make airways narrower) or dilate (relax to make airways wider); bronchi divide into smaller bronchioles within the lung tissue.

BRONCHIECTASIS An abnormal condition of the bronchial tree, characterized by irreversible widening and destruction of the bronchial walls of the lungs.

BRUCH'S MEMBRANE A membrane in the eye between the choroid membrane and the retina.

BRUTON TYROSINE KINASE (BTK) An enzyme vital for the maturation of B cells.

BULBAR MUSCLES Muscles that control chewing, swallowing, and speaking.

BUPHTHALMOS A characteristic enlargement of one or both eyes associated with infantile glaucoma.

C

C1 INHIBITOR Abbreviated C1-INH, this protein is responsible for preventing the action of the C1 complement molecules in the body. It is this protein that is either deficient or malformed in HANE.

CA-125 (CARBOHYDRATE ANTIGEN 125) A protein that is sometimes high when ovarian cancer is present. A blood sample can determine the level of CA-125 present.

CAFÉ-AU-LAIT SPOTS Birthmarks that may appear anywhere on the skin; named after the French coffee drink because of the light-brown color of the marks.

CALCIFICATION A process in which tissue becomes hardened due to calcium deposits.

CALCITRIOL A substance that assists in bone growth by helping to maintain calcium and phosphate levels in the blood. Vitamin D is converted into this substance by the body.

CALCIUM One of the elements that make up the hydroxyapatite crystals found in bone.

CAMPTODACTYLY An abnormal permanent bending of one or more fingers or toes.

CANAVAN DISEASE A serious genetic disease more common in the Eastern European Jewish population that causes mental retardation and early death. Canavan disease is caused by the lack of an enzyme called aspartoacylase.

CANCER A disease caused by uncontrolled growth of the body's cells.

CANCER CELLS Have characteristics that distinguish them from normal cells and non-cancerous cells; they are threatening, harmful, and resistant to treatment.

CANDIDATE GENE A gene that encodes proteins believed to be involved in a particular disease process.

CARBOHYDRATE Any of various natural compounds of carbon, hydrogen, and oxygen (as in sugars and starches) that are burned by the body for energy.

CARCINOGEN Any substance capable of causing cancer by mutating the cell's DNA.

CARCINOMA Any cancer that arises in the epithelium, the tissue that lines the external and internal organs of the body.

CARDIAC CONDUCTION DEFECT Abnormality of the electrical system of the heart, which regulates the heart beat.

CARDIAC MUSCLE The muscle of the heart.

CARDINAL SYMPTOMS A group of symptoms that define a disorder or disease.

CARDIOMYOPATHY A thickening of the heart muscle.

CARNITINE An amino acid necessary for metabolism of the long-chain fatty acid portion of lipids. Also called vitamin B_7.

CARNITINE PALMITOYLTRANSFERASE (CPT) An enzyme that transfers a palmitoyl group. CPT is a major regulatory enzyme of lipid metabolism, required for the transport of long-chain fatty acids across the inner mitochondria membrane. This transport depends on carnitine.

CARRIER A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

CARRIER TESTING Testing performed to determine if someone possesses one changed copy and one unchanged copy of a particular gene.

CARTILAGE Supportive connective tissue that cushions bone at the joints or that connects muscle to bone.

CASEIN HYDROLYSATE A preparation made from the milk protein casein, which is hydrolyzed to break it down into its constituent amino acids. Amino acids are the building blocks of proteins.

CAT (CT) SCAN Computerized (axial) tomography. A special x ray technique used to examine various tissues, particularly the brain, in great detail.

CATAGEN The breakdown phase of the hair growth cycle.

CATALYST A substance that changes the rate of a chemical reaction, but is not physically changed by the process.

CATALYZE Facilitate. A catalyst lowers the amount of energy required for a specific chemical reaction to occur. Catalysts are not used up in the chemical reactions they facilitate.

CATAPLEXY A symptom of narcolepsy in which there is a sudden episode of muscle weakness triggered by emotions. The muscle weakness may cause the person's knees to buckle, or the head to drop. In severe cases, the patient may become paralyzed for a few seconds to minutes.

CATARACT A clouding of the eye lens or its surrounding membrane that obstructs the passage of light resulting in blurry vision. Surgery may be performed to remove the cataract.

CATATONIC BEHAVIOR Behavior characterized by muscular tightness or rigidity and lack of response to the environment. In some patients, rigidity alternates with excited or hyperactive behavior.

CATECHOLAMINES Biologically active compounds involved in the regulation of the nervous and cardiovascular systems, rate of metabolism, body temperature, and smooth muscle.

CATHETER A narrow, flexible tube used to create a pathway for introducing drugs, nutrients, fluids, or blood products into the body and/or for removing fluid or other substances from the body.

CATHETERIZATION The process of inserting a hollow tube into a body cavity or blood vessel.

CATIONIC TRYPSINOGEN GENE Gene known to cause hereditary pancreatitis when significantly altered.

CAUTERIZATION Process of burning tissue either with a laser or electric needle to stop bleeding or destroy damaged tissue.

CDKN2A* OR *P16 Gene, when altered, known to cause Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome and possibly increased pancreatic cancer risk.

CECUM The first part of the large bowel.

CELL The smallest living units of the body, which group together to form tissues and help the body perform specific functions.

CELL ADHESION MOLECULE Any one of several thousand proteins that together control the cell-to-cell communication that must take place in order for cells to migrate to their proper places, develop into the proper types of cells, and make the appropriate connections with other cells.

CELLULAR IMMUNITY A type of acquired immunity mediated by killer T-cells; important in fighting 'hidden' infections, such as those caused by cellular parasites and some viruses.

CENTRAL NERVOUS SYSTEM (CNS) In humans, the central nervous system is composed of the brain, the cranial nerves and the spinal cord. It is responsible for the coordination and control of all body activities.

CENTRAL VISION The ability to see objects located directly in front of the eye. Central vision is necessary for reading and other activities that require people to focus on objects directly in front of them.

CENTROMERE The centromere is the constricted region of a chromosome. It performs certain functions during cell division.

CEREBELLAR ATAXIA Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

CEREBELLUM A portion of the brain consisting of two cerebellar hemispheres connected by a narrow vermis. The cerebellum is involved in control of skeletal muscles and plays an important role in the coordination of voluntary muscle movement. It interrelates with other areas of the brain to facilitate a variety of movements, including maintaining proper posture and balance, walking, running, and fine motor skills, such as writing, dressing, and eating.

CEREBRAL CORTEX The outer surface of the cerebrum made up of gray matter and involved in higher thought processes.

CEREBRAL PALSY Movement disability resulting from nonprogressive brain damage.

CEREBRAL VENTRICLES Spaces in the brain that are located between portions of the brain and filled with cerebrospinal fluid.

CEREBRO Related to the head or brain.

CEREBROSIDES Fatty carbohydrates that occur in the brain and nervous system.

CEREBROSPINAL FLUID Fluid that circulates throughout the cerebral ventricles and around the spinal cord within the spinal canal.

CEREBRUM The largest section of the brain, which is responsible for such higher functions as speech, thought, vision, and memory.

CEROID The by-product of cell membrane breakdown.

CERULOPLASMIN A protein circulating in the bloodstream that binds with copper and transports it.

CERVICAL DYSTONIA A focal dystonia that causes neck muscles to contract involuntarily—leading to abnormal movements and posture of the head and neck. Also known as spasmodic torticollis.

CERVICITIS Inflammation of the cervix.

CERVICO-MEDULLARY JUNCTION The area where the brain and spine connect.

CFTR Cystic fibrosis transmembrane conductance regulator. The protein responsible for regulating chloride movement across cells in some tissues. When a person has two abnormal copies of the CFTR gene, cystic fibrosis is the result.

CGG OR CGG SEQUENCE Shorthand for the DNA sequence: cytosine-guanine-guanine. Cytosine and guanine are two of the four molecules, otherwise called nucleic acids, that make up DNA.

CHAPERONIN A molecule that captures and refolds misshapen proteins that might interfere with normal cellular functions; also called a protein cage.

CHEMOTHERAPY Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

CHIARI II ANOMALY A structural abnormality of the lower portion of the brain (cerebellum and brain stem) associated with spina bifida. The lower structures of the brain are crowded and may be forced into the foramen magnum, the opening through which the brain and spinal cord are connected.

CHOANAL ATRESIA A bony or membranous blockage of the passageway between the nose and pharynx at birth.

CHOLESTEROL A fatty-like substance that is obtained from the diet and produced by the liver. Cells require cholesterol for their normal daily functions.

CHONDROCYTE A specialized type of cell that secretes the material which surrounds the cells in cartilage.

CHONDROSARCOMA A malignant tumor derived from cartilage cells.

CHOREA Involuntary, rapid, jerky movements.

CHOREOATHETOSIS Involuntary rapid, irregular, jerky movements or slow, writhing movements that flow into one another.

CHORIOCAPILLARIS Capillary layer of the choroid.

CHORION The outer membrane of the amniotic sac. Chorionic villi develop from its outer surface early in pregnancy. The villi establish a physical connection with the wall of the uterus and eventually develop into the placenta.

CHORIONIC VILLI A portion of the placenta that can be sampled at 10-12 weeks of pregnancy for the purposes of diagnosis.

CHORIONIC VILLUS SAMPLING (CVS) A procedure used for prenatal diagnosis at 10-12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases. Also known as chorionic villus biopsy.

CHOROID A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

CHOROID PLEXUS Specialized cells located in the ventricles of the brain that produce cerebrospinal fluid.

CHROMATID Each of the two strands formed by replication of a chromosome. Chromatids are held together by the centromere until the centromere divides and separates the two chromatids into a single chromosome.

CHROMOSOMAL ANEUPLODIES A condition in which the chromosomal number is either increased or decreased.

CHROMOSOME A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

CHROMOSOME DELETION A missing sequence of DNA or part of a chromosome.

CHROMOSOME INVERSION Rearrangement of a chromosome in which a section of a chromosome breaks off and rejoins the chromosome upside down.

CHROMOSOME TRANSLOCATION The exchange of genetic material between chromosomes, which can lead to extra or missing genetic material.

CHRONIC ATROPHIC GASTRITIS Irritation and break down of the stomach wall over a period of time.

CHYLOMICRON A type of lipoprotein made in the small intestine and used for transporting fats to other tissues in the body.

CILIARY BODY A structure within the eye that produces aqueous humor.

CIRCUMCISION The surgical removal of the foreskin of the penis.

CIRRHOSIS A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue.

Cirrhosis is a major risk factor for the later development of liver cancer.

CLASS I MHC Includes HLA-A, HLA-B, and HLA-C. Important in cellular immunity.

CLASS II MHC HLA-DP, HLA-DQ, and HLA-DR. Important in humoral immunity.

CLASS III MHC Includes the complement system.

CLAUDICATION Pain in the lower legs after exercise caused by insufficient blood supply.

CLAVICLE Also called the collarbone. Bone that articulates with the shoulder and the breast bone.

CLEFT An elongated opening or slit in an organ.

CLEFT LIP A separation of the upper lip that is present from birth but originates early in fetal development. A cleft lip may appear on one side (unilateral) or both sides (bilateral) and is occasionally accompanied by a cleft palate. Surgery is needed to completely repair cleft lip.

CLEFT PALATE A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

CLINICAL BREAST EXAM (CBE) Examination of the breasts, performed by a physician or nurse.

CLINICAL TRIAL The testing of a drug or some other type of therapy in a specific population of patients.

CLINODACTYLY An abnormal inward curving of the fingers or toes.

CLONE A cell or organism derived through asexual (without sex) reproduction containing the identical genetic information of the parent cell or organism.

CLOSED-ANGLE GLAUCOMA An increase in the fluid pressure within the eye due to a complete, and sometimes sudden, blockage of the fluid drainage passages.

CLUBFOOT Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

CO-DOMINANT Describes the state when two alleles of the same gene are both expressed when inherited together.

CO-ENZYME A small molecule such as a vitamin that works together with an enzyme to direct a biochemical reaction within the body.

COAGULATION The process by which a liquid becomes a solid, as in blood clotting.

COAGULOPATHY A disorder in which blood is either too slow or too quick to coagulate (clot).

COARCTATION A narrowing of the aorta that is often associated with bicuspid aortic valve.

COBB ANGLE A measure of the curvature of scoliosis, determined by measurements made on x rays.

COCHLEA A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

COCHLEAR IMPLANTATION A surgical procedure in which a small electronic device is placed under the skin behind the ear and is attached to a wire that stimulates the inner ear, allowing people who have hearing loss to hear useful sounds.

COFACTOR A substance that is required by an enzyme to perform its function.

COGNITION The mental activities associated with thinking, learning, and memory.

COGNITIVE/BEHAVIORAL THERAPIES Psychological counseling that focuses on changing the behavior of the patient.

COLCHICINE A compound that blocks the assembly of microtubules–protein fibers necessary for cell division and some kinds of cell movements, including neutrophil migration. Side effects may include diarrhea, abdominal bloating, and gas.

COLECTOMY Surgical removal of the colon.

COLITIS Inflammation of the colon.

COLLAGEN The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

COLOBOMA A birth disorder in which part of the eye is absent or does not form completely.

COLON The large intestine.

COLONOSCOPY Procedure for viewing the large intestine (colon) by inserting an illuminated tube into the rectum and guiding it up the large intestine.

COLORECTAL Of the colon and/or rectum.

COLOSTOMY The creation of an artificial opening into the colon through the skin for the purpose of removing bodily waste. Colostomies are usually required because key portions of the intestine have been removed.

COMPLEMENT SYSTEM Class III MHC (major histocompatobility complex) proteins capable of destroying invading organisms directly via natural immunity, as well as indirectly through an interaction with other components of the immune system.

COMPOUND HETEROZYGOTE Having two different mutated versions of a gene.

COMPUTED TOMOGRAPHY (CT) SCAN An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

COMT INHIBITORS Drugs that block catechol-O-methyltransferase, an enzyme that breaks down dopamine. COMT inhibitors include entacapone and tolcapone.

CONCEPTUS The products of conception, or the union of a sperm and egg cell at fertilization.

CONCORDANCE When two individuals have the same disease, such as when identical twins both have diabetes.

CONDUCTIVE HEARING LOSS Hearing loss that is the result of a dysfunction of the parts of the ear responsible for collecting sound. In this type of hearing loss, the auditory nerve is generally not damaged.

CONES Receptor cells that allow the perception of colors.

CONGENITAL Refers to a disorder that is present at birth.

CONGENITAL HEART DISEASE Structural abnormality of the heart at birth. Examples include a ventricular septal defect and atrial septal defect.

CONGENITAL HYPOPLASTIC ANEMIA (CHA) A significant reduction in the number of red blood cells present at birth, usually referring to deficient production of these cells in the bone marrow. Also sometimes called congenital aplastic anemia.

CONNECTIVE TISSUE A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

CONNEXIN A protein that joins cells together and allows them to exchange small substances.

CONOTRUNCAL HEART ABNORMALITY Congenital heart disorders primarily involving the ventricular (lower chambers) outflow tracts of the heart; includes subarterial ventricular septal defect, pulmonic valve atresia and stenosis, tetralogy of Fallot, and truncus arteriosus.

CONSANGUINEOUS Sharing a common bloodline or ancestor.

CONSANGUINITY A mating between two people who are related to one another by blood.

CONTINENCE Normal function of the urinary bladder and urethra, allowing fluid flow during urination and completely stopping flow at other times.

CONTINGUOUS GENE DELETION SYNDROME A genetic disorder due to the deletion of a number of genes that lie close to one another on a specific chromosome.

CONTINGUOUS GENE SYNDROME Conditions that occur as a result of microdeletions or microduplications involving several neighboring genes.

CONTRACTURE A tightening of muscles that prevents normal movement of the associated limb or other body part.

CONVULSION Involuntary contractions of body muscles that accompany a seizure episode.

COPROLALIA The involuntary expression of obscene words or phrases.

COPROPRAXIA The involuntary display of unacceptable/obscene gestures.

CORDOCENTESIS A prenatal diagnostic test, usually done between 16-30 weeks of gestation. Using ultrasound guidance, a thin needle is introduced through the abdomen into the amniotic sac. A blood sample is taken directly from the umbilical cord. Tests can then be done on the blood sample.

CORNEA The transparent structure of the eye over the lens that is continous with the sclera in forming the outermost, protective, layer of the eye.

CORNEAL TRANSPLANT Removal of impaired and diseased cornea and replacement with corneal tissue from a recently deceased person.

CORONAL SUTURE Skull suture that lies behind the forehead area, across the head from left side to the right side.

CORPORA ALBICANTIA Plural of corpus albicans. The scar tissue that remains on an ovarian follicle after ovulation.

CORPUS CALLOSUM A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

CORTICOSPINAL TRACT A bundle of long nerve fibers that runs from the motor control region of the cerebral cortex to the spinal cord, where it connects to nerves that control movement in the legs.

CORTICOSTEROIDS Anti-inflammatory medications. Related to cortisol, a naturally produced hormone that controls many body functions.

COXA VARA A deformed hip joint in which the neck of the femur is bent downward.

CRANIAL NERVES The twelve nerves that originate in the brain and control functions such as hearing, vision and facial expression.

CRANIAL SUTURE Any one of the seven fibrous joints between the bones of the skull.

CRANIOFACIAL Relating to or involving both the head and the face.

CRANIOPAGUS Conjoined twins with separate bodies and one shared head.

CRANIOPHARYNGIOMA A tumor near the pituitary gland in the craniopharyngeal canal that often results in intracranial pressure.

CRANIOSYNOSTOSIS Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

CRANIUM The skeleton of the head, which includes all of the bones of the head except the mandible.

CREATININE A waste product of the body found in the urine. It is useful in determining the overall kidney function.

CREUTZFELDT-JAKOB DISEASE A degenerative disease of the central nervous system caused by a prion, or "slow virus."

CRI DU CHAT SYNDROME A syndrome caused by a deletion in chromosome 5; characterized by a strange cry that sounds like the mewing of a cat.

CRYPTOPHTHALMOS An abnormal formation of the eye in which the eyelid, or overlaying skin of the eye, is fused shut. Literally, "hidden eye."

CRYPTORCHIDISM A condition in which one or both testes fail to descend normally.

CURETTAGE A surgical scrapping or cleaning.

CUTANEOUS Of, pertaining to, or affecting the skin.

CUTANEOUS SYNDACTYLY Fusion of the soft tissue between fingers or toes resulting in a webbed appearance.

CYANOSIS/CYANOTIC The bluish color of the skin that occurs when there is very low oxygen in the blood that is being transported throughout the body.

CYDROCEPHALY Excessive accumulation of cerebral spinal fluid in the brain ventricles.

CYST An abnormal sac or closed cavity filled with liquid or semisolid matter.

CYSTIC FIBROSIS A respiratory disease characterized by chronic lung disease, pancreatic insufficiency, and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encode a transmembrane receptor.

CYSTIC HYGROMA An accumulation of fluid behind the fetal neck, often caused by improper drainage of the lymphatic system *in utero*.

CYSTINE A sulfur-containing amino acid, sometimes found as crystals in the kidneys or urine, that forms when proteins are broken down by digestion.

CYTOKINE A protein associated with inflammation that, at high levels, may be toxic to nerve cells in the developing brain.

CYTOKINES Proteins released by helper T-cells that stimulate and support immune responses (inflammation) mediated by B-cells and killer T-cells. At high levels, cytokines may be toxic to nerve cells in the developing brain.

CYTOPLASM The substance within a cell including the organelles and the fluid surrounding the nucleus.

CYTOSKELETON The network of proteins underlying and maintaining the integrity of the red blood cell membrane.

D

DANDY-WALKER MALFORMATION A complex structural abnormality of the brain frequently associated with hydrocephalus, or accumulation of excess fluid in the brain. Abnormalities in other areas of the body may also be present. Individuals with Dandy-Walker malformation have varying degrees of mental handicap or none at all.

DECIDUOUS TEETH The first set of teeth or "baby teeth."

DECREASED PENETRANCE Individuals who inherit a changed disease gene but do not develop symptoms.

DEEP VEIN THROMBOSIS A blood clot in one of the systemic veins deep in the body.

DEGENERATION Nerves progressively withering.

DEGENERATIVE DISC DISEASE Narrowing of the disc space between the spinal bones (vertebrae).

DEGENERATIVE DISORDER A disorder by which the body or a part of the body gradually loses its ability to fucntion.

DEGRADATION Loss or diminishing.

DEHYDRATION An extreme loss of water in the body which, if untreated, can lead to brain damage and death.

DELAYED BONE AGE An abnormal condition in which the apparent age of the bones, as seen in x rays, is less than the chronological age of the patient.

DELETION The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

DELIRIUM A disturbance of consciousness marked by confusion, difficulty paying attention, delusions, hallucinations, or restlessness. It can be distinguished from dementia by its relatively sudden onset and variation in the severity of the symptoms.

DELUSION A fixed, false belief that is resistant to reason or factual disproof.

DEMENTIA A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

***DE NOVO* MUTATION** Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

***DE NOVO* DELETION** A deletion that occurs for the first time in the affected individual. The cause of *de novo* deletions is not known.

DEOXYRIBONUCLEIC ACID (DNA) The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DEPIGMENTATION Loss of pigment or skin color.

DEPOLARIZATION The dissipation of an electrical charge through a membrane.

DEPOT DOSAGE A form of medication that can be stored in the patient's body tissues for several days or weeks, thus minimizing the risk of the patient forgetting daily doses. Haloperidol and fluphenazine can be given in depot form.

DEPRIVATIONAL DWARFISM A condition where emotional disturbances are associated with growth failure and abnormalities of pituitary function.

DERMATOLOGIST A physician that specializes in disorders of the skin.

DERMATOSPARAXIS Skin fragility caused by abnormal collagen.

DERMIS The layer of skin beneath the epidermis.

DESCEMET'S MEMBRANE Sheet of tissue that lies under the stroma and protects against infection and injuries.

DESFEROXAMINE The primary drug used in iron chelation therapy. It aids in counteracting the life-threatening buildup of iron in the body associated with long-term blood transfusions.

DESMOID TUMOR Benign, firm mass of scar-like connective tissue

DESMOPRESSIN (DDAVP) A drug used in the treatment of von Willebrand disease.

DEUTERANOPIA The inability or difficulty in distinguishing red/green colors.

DEVELOPMENT The process whereby undifferentiated embryotic cells replicate and differentiate into limbs, organ systems, and other body components of the fetus.

DEVELOPMENTAL DELAY When children do not reach certain milestones at appropriate ages. For example, a child should be able to speak by the time he or she is five years old.

DEVELOPMENTAL MILESTONES Infants and toddlers develop skills at certain ages. For example, by nine months, a child should be able to grasp and toss a bottle.

DEXTROCARDIA Disorder in which the position of the heart is the mirror image of its normal position.

DIABETES An inability to control the levels of sugar in the blood due to an abnormality in the production of, or response to, the hormone insulin.

DIABETES MELLITUS The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

DIAGNOSTIC TESTING Testing performed to determine if someone is affected with a particular disease.

DIALYSIS Process by which special equipment purifies the blood of a patient whose kidneys have failed.

DIAPHYSIS The middle portion, or shaft, of a long bone.

DIARRHEA Loose, watery stool.

DIASTOLIC BLOOD PRESSURE Blood pressure when the heart is resting between beats.

DICEPHALUS Conjoined twins who share one body but have two separate heads and necks.

DIFFERENTIATE Specialized development to perform a particular function.

DIGESTIVE ENZYME Proteins secreted by the pancreas that enter the small intestine and break down food so it can be absorbed by the body.

DIGIT A finger or toe. Plural–digits.

DIHYDROTESTOSTERONE (DHT) A male sex hormone formed from testosterone by the enzyme 5-alpha-reductase. DHT causes hair follicles to shut down, shortening the growth phase of the hair growth cycle and leading to miniaturization.

DILATED CARDIOMYOPATHY A diseased and weakened heart muscle that is unable to pump blood efficiently.

DIOPTER (D) A unit of measure for describing refractive power.

DIPLEGIA Paralysis affecting like parts on both sides the body, such as both arms or both legs.

DIPLOID Means "double number." The normal number of chromosomes (two) for all cells of the human body, except for the sex cells.

DISTAL Away from the point of origin.

DISTAL ARTHROGRYPOSIS A disorder characterized by contractions of the muscles in the hands.

DISTAL MUSCLES Muscles that are furthest away from the center of the body.

DISTAL MUSCULAR DYSTROPHY (DD) A form of muscular dystrophy that usually begins in middle age or later, causing weakness in the muscles of the feet and hands.

DISULFIRAM A medication that has been used since the late 1940s as part of a treatment plan for alcohol abuse. Disulfiram, which is sold under the trade name Antabuse, produces changes in the body's metabolism of alcohol that cause headaches, vomiting, and other unpleasant symptoms if the patient drinks even small amounts of alcohol.

DIURETICS Medications that increase the excretion of urine.

DIVERTICULAE Sacs or pouches in the walls of a canal or organ. They do not normally occur, but may be acquired or present from birth. Plural form of diverticula.

DIZYGOTIC From two zygotes, as in non-identical, or fraternal twins. The zygote is the first cell formed by the union of sperm and egg.

DNA MUTATION ANALYSIS A direct approach to the detection of a specific genetic mutation or mutations using one or more laboratory techniques.

DNA REPEATS A three letter section of DNA, called a triplet, which is normally repeated several times in a row. Too many repeats often cause the gene to not function properly, resulting in disease.

DNA TESTING Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

DOMINANT A trait that is expressed equally in homozygous, heterozygous, and hemizygous individuals.

DOMINANT GENE A gene, whose presence as a single copy, controls the expression of a trait.

DOMINANT INHERITANCE A type of genetic inheritance pattern that results in one form of a gene being dominant over other forms. Therefore, the dominant allele can express itself and cause disease, even if only one copy is present.

DOMINANT PROGRESSIVE HEARING LOSS The main type of non-syndromic progressive sensorineural hearing loss seen in humans.

DOMINANT TRAIT A genetic trait where one copy of the gene is sufficient to yield an outward display of the trait; dominant genes mask the presence of recessive genes; dominant traits can be inherited from a single parent.

DOPAMINE A neurochemical made in the brain that is involved in many brain activities, including movement and emotion.

DOPAMINE RECEPTOR ANTAGONISTS (DAS) The older class of antipsychotic medications, also called neuroleptics. These primarily block the site on nerve cells that normally receive the brain chemical dopamine.

DORSAL RHIZOTOMY A surgical procedure that cuts nerve roots to reduce spasticity in affected muscles.

DORSAL ROOT GANGLIA The subset of neuronal cells controlling impulses in and out of the brain.

DOWN SYNDROME A genetic condition characterized by moderate to severe mental retardation, a characteristic facial appearance, and, in some individuals, abnormalities of some internal organs. Down syndrome is always caused by an extra copy of chromosome 21, or three rather than the normal two. For this reason, Down syndrome is also known as *trisomy 21*.

DOWNSHOOT Downward movement of the eye.

DRPLA Dentatorubral-pallidoluysian atrophy; also called Haw River syndrome and Natito-Oyanagi disease. DRPLA is a disorder of ataxia, choreoathetosis, and dementia in adults, and ataxia, myoclonus, epilepsy, and mental retardation in children.

DRUSEN Fatty deposits that can accumulate underneath the retina and macula, and sometimes lead to age-related macular degeneration (AMD). Drusen formation can disrupt the photoreceptor cells, which causes central and color vision problems for people with dry AMD.

DUCHENNE MUSCULAR DYSTROPHY (DMD) The most severe form of muscular dystrophy, DMD usually affects young boys and causes progressive muscle weakness, usually beginning in the legs.

DUCT Tube-like structure that carries secretions from glands.

DUCTUS The blood vessel that joins the pulmonary artery and the aorta. When the ductus does not close at birth, it causes a type of congenital heart disease called patent ductus arteriosus.

DUCTUS ARTERIOSUS The temporary channel or blood vessel between the aorta and pulmonary artery in the fetus.

DUODENUM Portion of the small intestine nearest the stomach; the first of three parts of the small intestine.

DUPLICATION A chromosomal abnormality in which a broken segment of a chromosome attaches to the chromosome pair resulting in extra chromosomal material.

DWARFISM Any condition that results in extremely shortened limbs.

DYSARTHRIA Slurred speech.

DYSGENESIS Abnormal formation of an organ or part usually occuring during embryonic development.

DYSKINESIA Impaired ability to make voluntary movements.

DYSMORPHIC FEATURE A subtle change in appearance such as low set ears or a flattened nasal bridge that suggests a genetic syndrome may be present.

DYSOSTOSIS MULTIPLEX A variety of bone and skeletal malformations.

DYSPHORIA Feelings of anxiety, restlessness, and dissatisfaction.

DYSPLASIA/DYSPLASTIC The abnormal growth or development of a tissue or organ.

DYSTHYMIA A psychological condition of chronic depression that is not disabling, but prevents the patient from functioning at his or her full capacity.

DYSTONIA Painful involuntary muscle cramps or spasms.

DYSTOPIA CANTHORUM A wide spacing between the inner corners of the eyes, with the eyes themselves having normal spacing. Also called telecanthus.

DYSTROPHIN A protein that helps muscle tissue repair itself. Both Duchenne muscular dystrophy and Becker muscular dystrophy are caused by flaws in the gene that instructs the body how to make this protein.

E

EAR TAGS Excess pieces of skin on the outside of the ear.

EARLY ON-SET DYSTONIA Dystonia that begins in adolescence. Most common among Jews of Eastern European ancestry.

E-CADHERIN/CDH1 A gene involved in cell-to-cell connection. Alterations in this gene have been found in several families with increased rates of gastric cancer.

ECHOCARDIOGRAM A non-invasive technique, using ultrasonic waves, used to look at the various structures and function of the heart.

ECHOCARDIOGRAPH A record of the internal structures of the heart obtained from beams of ultrasonic waves directed through the wall of the chest.

ECHOLALIA Involuntary echoing of the last word, phrase, or sentence spoken by someone else or sound in the environment.

ECHOPRAXIA The imitation of the movement of another individual.

ECTODERM The outermost of the three embryonic cell layers, which later gives rise to the skin, hair, teeth, and nails.

ECTODERMAL DYSPLASIA A hereditary condition that results in the malformation of the skin, teeth, and hair. It is often associated with malfunctioning or absent sweat glands and/or tear ducts.

ECTOPIA LENTIS Dislocation of the lens of the eye. It is one of the most important single indicators in diagnosing Marfan syndrome.

ECTOPIC Tissue found in an abnormal location.

ECTRODACTYLY A birth defect involving a split or cleft appearance of the hands and/or feet, also referred to as a "lobster-claw malformation."

ECZEMA Inflammation of the skin with redness and other variable signs such as crusts, watery discharge, and itching.

EDEMA Extreme amount of watery fluid that causes swelling of the affected tissue.

EDWARDS SYNDROME A syndrome caused by trisomy 18; characterized by multi-system disorders; and usually lethal by age one.

EFFLUVIUM The medical term for massive hair loss or shedding.

ELASTIC FIBER Fibrous, stretchable connective tissue made primarily from proteins, elastin, collagen, and fibrillin.

ELASTIN A protein that gives skin the ability to stretch and then return to normal.

ELECTROCARDIOGRAM (ECG, EKG) A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

ELECTROCONVULSIVE THERAPY A psychological treatment in which a series of controlled electrical impulses are delivered to the brain in order to induce a seizure within the brain.

ELECTROLYTE A solution or a substance in a solution consisting of various chemicals that can carry electric charges. They exist in the blood as acids, bases, and salts, such as sodium, calcium, potassium, chlorine, and magnesium.

ELECTROMYOGRAPHY (EMG) A test that uses electrodes to record the electrical activity of muscle. The information gathered is used to diagnose neuromuscular disorders.

ELECTRORETINOGRAPHY (ERG) A diagnostic test that records electrical impulses created by the retina when light strikes it.

EMBOLIZATION THERAPY Introduction of various substances into the circulation to plug up blood vessels in order to stop bleeding.

EMBRYO The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

EMOLLIENT Petroleum or lanolin based skin lubricants.

EMPHYSEMA A chronic lung disease that begins with breathlessness during exertion and progresses to shortness of breath at all times, caused by destructive changes in the lungs.

ENCAPSULATED Referring to bacteria that have a thick capsule protecting their cell wall.

ENCEPHALOCELE A gap in the skull through which membranes and brain tissue may protrude.

ENCHONDROMAS Benign cartilaginous tumors arising in the cavity of bone. They have the possibility of causing lytic destruction within the bone.

ENDOCARDITIS A dangerous infection of the heart valves caused by certain bacteria.

ENDOCRINE SYSTEM A system of ductless glands that regulate and secrete hormones directly into the bloodstream.

ENDOLYMPH The fluid in the inner ear.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP) A method of viewing the pancreas by inserting a thin tube down the throat into the pancreatic and bile ducts, injection of dye and performing x rays.

ENDOSCOPY A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

ENDOSTEAL Relating to the endosteum, which is the lining of the medullary cavity.

ENDOTHELIAL CELLS The cells lining the inner walls of the blood vessels.

ENDOTHELIUM Extremely thin innermost layer of the cornea.

ENLARGED VESTIBULAR AQUEDUCT (EVA) An enlargement of a structure inside the inner ear called the vestibular aqueduct, which is a narrow canal that allows fluid to move within the inner ear. EVA is seen in approximately 10% of people who have sensorineural hearing loss.

ENTEROCOLITIS Severe inflammation of the intestines that affects the intestinal lining, muscle, nerves, and blood vessels.

ENTEROSCOPY A procedure used to examine the small intestine.

ENTEROVIRUS Any of a group of viruses that primarily affect the gastrointestinal tract.

ENTHESITIS Inflammation at the place where the ligaments insert into the bone.

ENTHESOPATHY Disorder of the ligament attachment to the bone.

ENZYMATIC/ENZYME REPLACEMENT THERAPY A treatment method used to replace missing enzymes. It is possible to synthesize enzymes and then inject them intravenously into patients.

ENZYME A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

ENZYME EFFICIENCY The rate at which an enzyme can perform the chemical transformation it is expected to accomplish. This is also called turnover rate.

EPENDYMOMA Tumor of the central nervous system derived from cells that line the central canal of the spinal cord and the ventricles of the brain.

EPIBULBAR DERMOIDS Cysts on the eyeball.

EPICANTHAL FOLD Fold of skin extending from the eyelid over the inner corner of the eye.

EPIDERMIS The outermost layer of the skin.

EPIDERMOID CYST Benign, cystic tumor derived from epithelial cells.

EPIDIDYMUS Coiled tubules that are the site of sperm storage and maturation for motility and fertility. The epididymis connects the testis to the vas deferens.

EPILEPSY A seizure disorder.

EPIPHYSES The growth area at the end of a bone.

EPIPHYSIS The end of long bones, usually terminating in a joint.

EPITHELIAL CELLS The layer of cells that cover the open surfaces of the body such as the skin and mucous membranes.

EPITHELIUM The layer of cells that cover the open surfaces of the body such as the skin and mucous membranes.

ERYTHEMA Redness of the skin due to dilatation of capillaries.

ERYTHEMA NODOSUM LEPROSUM A complication of leprosy characterized by development of painful small swellings due to inflammation of a blood or lymph vessel. It is often accompanied by inflammation of a nerve or nerves, causing decreased function of the affected area.

ERYTHROPOIESIS The process through which new red blood cells are created; it begins in the bone marrow.

ERYTHROPOIETIC Referring to the creation of new red blood cells.

ESOPHAGUS The part of the digestive tract which connects the mouth and stomach; the foodpipe.

ESTROGEN A female sex hormone.

ETHANOL The chemical name for beverage alcohol. It is also sometimes called ethyl alcohol or grain alcohol to distinguish it from isopropyl or rubbing alcohol.

EUGENICS A social movement in which the population of a society, country, or the world is to be improved by controlling the passing on of hereditary information through mating.

EXCISION Surgical removal.

EXOCRINE PANCREAS The secreting part of the pancreas.

EXON The expressed portion of a gene. The exons of genes are those portions that actually chemically code for the protein or polypeptide that the gene is responsible for producing.

EXOSTOSIS An abnormal growth (benign tumor) on a bone.

EXTERNAL MEATUS The external opening through which urine and seminal fluid (in males only) leave the body.

EXTRAOCULAR MUSCLE FIBROSIS Abnormalities in the muscles that control eye movement.

EXTRAPYRAMIDAL SYMPTOMS (EPS) A group of side effects associated with antipsychotic medications. EPS include parkinsonism, akathisia, dystonia, and tardive dyskinesia.

F

FACIAL ASYMMETRY Term used to describe when one side of the face appears different than the other.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSH) This form of muscular dystrophy, also known as Landouzy-Dejerine condition, begins in late childhood to early adulthood and affects both men and women, causing weakness in the muscles of the face, shoulders, and upper arms.

FACTOR VIII A protein involved in blood clotting that requires vWF for stability and long-term survival in the bloodstream.

FACTORS Coagulation factors are substances in the blood, such as proteins and minerals, that are necessary for clotting. Each clotting substance is designated with roman numerals I through XIII.

FAILURE TO THRIVE Significantly reduced or delayed physical growth.

FALLOPIAN TUBE Either of a pair of tubes that conduct ova from the ovaries to the uterus.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP) Inherited syndrome causing large numbers of polyps and increased risk of colon cancer and other cancers.

FAMILIAL GASTRIC CANCER Gastric cancer that occurs at a higher rate in some families.

FANCONI SYNDROME A reabsorbtion disorder in the kidney tubules.

FASCICULATIONS Involuntary twitching of a patient's muscles.

FATTY ACIDS The primary component of fats (lipids) in the body. Carnitine palmitoyl transferase (CPT) deficiency involves abnormal metabolism of the long-chain variety of fatty acids.

FECAL (OCCULT) BLOOD TEST Study of stool (feces) to identify loss of blood in the gastrointestinal system.

FETAL ALCOHOL SYNDROME Syndrome characterized by distinct facial features and varying mental retardation in an infant due to impaired brain develop-

ment resulting from the consumption of alcohol during pregnancy.

FETAL HYDROPS A condition in which there is too much fluid in the fetal tissues and/or cavities.

FETOSCOPY A technique by which a developing fetus can be viewed directly using a thin, flexible optical device (fetoscope) inserted into the mother's uterus.

FETUS The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term embryo is used prior to the third month.

FETUS IN FETU In this case, one fetus grows inside the body of the other twin.

FIBRILLATION A rapid, irregular heartbeat.

FIBRILLIN-2 A protein that forms part of the body's connective tissue. The precise function of fibrillin-2 is not known.

FIBRIN The final substance created through the clotting cascade, which provides a strong, reliable plug to prevent further bleeding from the initial injury.

FIBRINOGEN A fibrous protein that circulates in blood and participates in blood clotting by attaching to platelets.

FIBROBLAST Cells that form connective tissue fibers like skin.

FIBROBLAST GROWTH FACTOR RECEPTOR GENE A type of gene that codes for a cell membrane receptor involved in normal bone growth and development.

FIBROID/FIBROMA A non-cancerous tumor of connective tissue made of elongated, threadlike structures, or fibers, which usually grow slowly and are contained within an irregular shape. Fibroids are firm in consistency but may become painful if they start to break down or apply pressure to areas within the body. They frequently occur in the uterus and are generally left alone unless growing rapidly or causing other problems. Surgery is needed to remove fibroids.

FIBROSIS The abnormal development of fibrous tissue; scarring.

FINASTERIDE An oral medication used to treat male pattern hair loss. Finasteride, sold under the trade names Proscar and Propecia, is an androgen inhibitor.

FINE NEEDLE ASPIRATION (FNA) Insertion of a thin needle through the skin to an area of sample tissue.

FIRST-DEGREE RELATIVE A parent, child, or sibling is a first degree relative. First-degree relatives have one half of their genes in common.

FIRST-RANK SYMPTOMS A set of symptoms designated by Kurt Schneider in 1959 as the most important diagnostic indicators of schizophrenia. These symptoms include delusions, hallucinations, thought insertion or removal, and thought broadcasting. First-rank symptoms are sometimes referred to as Schneiderian symptoms.

FISH (FLUORESCENCE *IN SITU* HYBRIDIZATION) Technique used to detect small deletions or rearrangements in chromosomes by attempting to attach a fluorescent (glowing) piece of a chromosome to a sample of cells obtained from a patient.

FISTULA An abnormal passage or communication between two different organs or surfaces.

FLEXION The act of bending or condition of being bent.

FLEXION CREASES The lines present on the palms of the hands and the soles of the feet from normal bending of these body parts. Some individuals affected with arthrogryposis lack these characteristic lines.

FMR-1 GENE A gene found on the X chromosome. Its exact purpose is unknown, but it is suspected that the gene plays a role in brain development.

FOCAL SEIZURE A seizure that causes a brief and temporary change in movement, sensation, or nerve function.

FOLATE-SENSITIVE FRAGILE SITE A chromosome location which, under folate-deficient conditions, appears as a gap in the chromosome and is susceptible to breakage.

FOLLICLE A pouch-like depression.

FOLLICLE-STIMULATING HORMONE (FSH) A hormone that in females stimulates estrogen and in males stimulates sperm production.

FONTANELLE One of several "soft spots" on the skull where the developing bones of the skull have yet to fuse.

FORAMEN A small opening or hole in a body part or tissue. Dandy-Walker malformation is characterized by the absence or failure to develop the three foramina in the fourth ventricle of the brain.

FOUNDER EFFECT Increased frequency of a gene mutation in a population that was founded by a small ancestral group of people, at least one of whom was a carrier of the gene mutation.

FRAGILE X SYNDROME A condition caused by an abnormality of a region on the X chromosome, which may be expressed in males or females, and may increase in severity when inherited from the mother.

FRIBRILLIN A protein that is an important part of the structure of the body's connective tissue. In Marfan syndrome, the gene responsible for fibrillin has mutated, causing the body to produce an abnormal protein.

FRONTAL BOSSING A term used to describe a rounded forehead with a receded hairline.

FRONTAL PLAGIOCEPHALY An abnormal condition of the skull in which the front is more developed on one side than it is on the other side.

G

GAIT A manner of walking.

GALACTITOL An alcohol derivative of galactose that builds up in the lens and causes cataracts.

GALACTOSE One of the two simple sugars, together with glucose, that makes up the protein, lactose, found in milk. Galactose can be toxic in high levels.

GALACTOSEMIA Abnormally high levels of galactose in the blood due to an inherited disorder in the conversion of galactose to glucose.

GALACTOSURIA High levels of galactose found in the urine that is seen with galactosemia.

GALLBLADDER A small, pear-shaped organ in the upper right hand corner of the abdomen. It is connected by a series of ducts (tube-like channels) to the liver, pancreas, and duodenum (first part of the small intestine). The gallbladder receives bile from the liver, and concentrates and stores it. After a meal, bile is squeezed out of the gallbladder into the intestine, where it aids in digestion of food.

GANGLIONEUROBLASTOMA A tumor of the nerve fibers and ganglion cells.

GANGLIOSIDE A fatty (lipid) substance found within the brain and nerve cells.

GANGRENE Death of a tissue, usually caused by insufficient blood supply and followed by bacterial infection of the tissue.

GASTRIC Associated with the stomach.

GASTRIC TUBE A tube that is surgically placed though the skin of the abdomen to the stomach so that feeding with nutritional liquid mixtures can be accomplished.

GASTROENTEROLOGIST A physician who specializes in disorders of the digestive system.

GASTROESPHAGEAL REFLUX The return of the contents of the stomach back up into the esophagus.

GASTROINTESTINAL Concerning the stomach and intestine.

GASTROINTESTINAL (GI) SYSTEM Body system involved in digestion, the breaking down and use of food.

GASTROSCHISIS A small abnormality in the abdominal wall normally located to the right of the umbilicus, and not covered by a membrane, where intestines and other organs may protrude.

GASTROSTOMY The construction of an artificial opening from the stomach through the abdominal wall to permit the intake of food.

GAUCHER DISEASE Autosomal recessive metabolic disorder caused by dysfunction of the lysosomal enzyme beta-glucosidase.

GAVAGE Feeding tube.

GENE A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

GENE THERAPY Replacing an abnormal gene with the normal copy.

GENE TRANSCRIPTION The process by which genetic information is copied from DNA to RNA, resulting in a specific protein formation.

GENETIC Referring to genes and characteristics inherited from parents.

GENETIC ANTICIPATION The tendency for an inherited disease to become more severe in successive generations.

GENETIC COUNSELOR A health professional with advanced training in genetics and psychology who educates people about genetic conditions and testing.

GENETIC DISEASE A disease that is (partly or completely) the result of the abnormal function or expression of a gene; a disease caused by the inheritance and expression of a genetic mutation.

GENETIC ENGINEERING The manipulation of genetic material to produce specific results in an organism.

GENETIC HETEROGENEITY The occurrence of the same or similar disease, caused by different genes among different families.

GENETIC SUSCEPTIBILITY The predisposition to a disease resulting from one or more genetic traits.

GENETIC TEST Testing of chromosomes and genes from an individual or unborn baby for a genetic condition. Genetic testing can only be done if the gene is known.

GENETICIST A specialist (M.D. or Ph.D.) who has training and certification in diagnosing, managing, and counseling individuals/families with genetic disorders. Genetic counselors hold a master's degree in medical genetics, and provide many of the same services as geneticists.

GENETICS The study of hereditary traits passed on through the genes.

GENITAL TRACT The organs involved in reproduction. In a male, they include the penis, testicles, prostate, and various tubular structures to transport seminal fluid and sperm. In a female, they include the clitoris, vagina, cervix, uterus, fallopian tubes, and ovaries.

GENITALS The internal and external reproductive organs in males and females.

GENITOURINARY Related to the reproductive and urinary systems of the body.

GENOME All of the DNA in one cell.

GERM LINE MOSAICISM A rare event that occurs when one parent carries an altered gene mutation that affects his or her germ line cells (either the egg or sperm cells) but is not found in the somatic (body) cells.

GERM-LINE GENE THERAPY The introduction of genes into reproductive cells or embryos to correct inherited genetic disorders that can cause disease.

GESTATIONAL DIABETES Diabetes of pregnancy that can be insulin- or non-insulin-dependent. Usually resolves following delivery, but may predispose to recurrent gestational diabetes and/or other forms of diabetes.

GILLBERG'S CRITERIA A six-item checklist for Asperger syndrome developed by Christopher Gillberg, a Swedish researcher. It is widely used as a diagnostic tool.

GLAUCOMA An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

GLIOBLASTOMA MULTIFORME Tumor of the central nervous system consisting of undifferentiated glial cells.

GLOBIN One of the component protein molecules found in hemoglobin. Normal adult hemoglobin has a pair each of alpha-globin and beta-globin molecules.

GLOBOID CELLS Large cells containing excess toxic metabolic "waste" of galactosylceramide and psychosine.

GLOMERULI Tiny clusters of capillaries in the kidney.

GLOMERULUS A structure in the kidney composed of blood vessels that are actively involved in the filtration of the blood.

GLUCOCEREBROSIDE A cerebroside that contains glucose in the molecule.

GLUCOSE One of the two simple sugars, together with galactose, that makes up the protein, lactose, found in milk. Glucose is the form of sugar that is used by the body to generate energy.

GLUTEN A protein found in wheat, rye, barley, and oats.

GLYCOGEN The chemical substance used by muscles to store sugars and starches for later use. It is composed of repeating units of glucose.

GLYCOLYSIS The pathway in which a cell breaks down glucose into energy.

GLYCOPROTEIN A protein with at least one carbohydrate group.

GLYCOPROTEIN IIB/IIIA (GP IIB/IIIA) Sugar-proteins on the surface of platelets that bind to the fibrous protein, fibrinogin. These sugar-proteins are abnormal in Glanzmann's thrombasthenia.

GLYCOSYLPHOSPHATIDYLINOSITOL (GPI) A fat that attaches proteins to the outside walls of blood cells.

GOITER An enlargement of the thyroid gland, causing tissue swelling that may be seen and/or felt in the front of the neck. May occur in people who have overactive production of thyroid hormones (hyperthyroidism), decreased production of thyroid hormones (hypothyroidism), or among people who have normal production of thyroid hormones.

GONAD The organ that will become either a testis (male reproductive organ) or ovary (female reproductive organ) during fetal development.

GONADOTROPHIN Hormones that stimulate the ovary and testicles.

GONIOSCOPE An instrument used to examine the trabecular meshwork; consists of a magnifier and a lens equipped with mirrors.

GRAFT-VERSUS-HOST DISEASE In bone marrow transplantation, the complication that occurs when the donor's cells attack the recipient's tissues, in part due to non-identical donor-recipient HLA types.

GRAND MAL SEIZURE A seizure that causes a loss of consciousness, a loss of bladder control, generalized muscle contractions, and tongue biting.

GRANULOCYTOPENIA A reduced number of white blood cells in the circulation.

GRAY MATTER Areas of the brain and spinal cord that are comprised mostly of unmyelinated nerves.

GREAT TOE The first and largest toe on the foot.

GRIEF REACTION The normal depression felt after a traumatic major life occurrence such as the loss of a loved one.

GROWTH HORMONE A hormone that eventually stimulates growth. Also called somatotropin.

GUSTATORY LACRIMATION Abnormal development of the tear ducts causing tears when chewing.

H

HALLUCAL POLYDACTYLY The appearance of an extra great toe.

HALLUCINATION A sensory experience of something that does not exist outside the mind. A person can experience a hallucination in any of the five senses. Auditory hallucinations are a common symptom of schizophrenia.

HALLUX The great toe.

HAMARTOMA An overgrowth of normal tissue.

HAPLOID Means "half the number;" the number of chromosomes in a sex cell.

HAPLOINSUFFICIENCY The lack of one of the two normal copies of a gene. Haploinsufficiency can result in a genetic disorder if normal function requires both copies of the gene and is one explanation for a dominant pattern of inheritance.

HAPLOTYPE A set of alleles that are inherited together as a unit on a single chromosome because of their close proximity.

HEAD TURN Habitual head position that has been adopted to compensate for abnormal eye movements.

HEARING THRESHOLD The minimum sound level at which a particular individual can hear. This is also called the hearing level (HL) of that person.

HEART VALVE One of four structures found within the heart that prevents backwards flow of blood into the previous chamber.

HEIMLICH MANEUVER An action designed to expel an obstructing piece of food from the throat. It is performed by placing the fist on the abdomen, underneath the breastbone, grasping the fist with the other hand (from behind), and thrusting it inward and upward.

***HELICOBACTER PYLORI* (*H. PYLORI*)** Bacterium that infects humans and may be associated with an increased risk of gastric cancer.

HELLER'S SYNDROME Another name for Childhood Disintegrative Disorder (CDD). It is also sometimes called dementia infantilis.

HELPER T-CELL Specialized white blood cell that assists in humoral and cellular immunity.

HEMANGIOBLASTOMA A tumor of the brain or spinal cord arising in the blood vessels of the meninges or brain.

HEMANGIOMA Benign tumor made up of clusters of newly formed blood vessels.

HEMATIN A drug administered intravenously to halt an acute porphyria attack. It causes heme biosynthesis to decrease, preventing the further accumulation of heme precursors.

HEMATOMA An accumulation of blood, often clotted, in a body tissue or organ, usually caused by a break or tear in a blood vessel.

HEMATOPOETIC GROWTH FACTORS Substances that assist in the formation of blood cells.

HEMATURIA The presence of blood in the urine.

HEME The iron-containing molecule in hemoglobin that serves as the site for oxygen binding.

HEMIFACIAL MICROSOMIA Term used to describe when one side of the face is smaller than the other.

HEMIHYPERPLASIA A condition in which overdevelopment or excessive growth of one half of a specific organ or body part on only one side of the body occurs.

HEMIHYPERTROPHY Asymmetric overgrowth in which there is an increase in size of existing cells.

HEMIPLEGIA Paralysis of one side of the body.

HEMIVERTEBRA A disorder in which one side or half of a vertebra fails to form.

HEMIZYGOUS Having only one copy of a gene or chromosome.

HEMOCHROMATOSIS Accumulation of large amounts of iron in the tissues of the body.

HEMOGLOBIN Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

HEMOGLOBIN A Normal adult hemoglobin that contains a heme molecule, two alpha-globin molecules, and two beta-globin molecules.

HEMOGLOBIN A1C TEST A screening test for diabetes.

HEMOGLOBIN ELECTROPHORESIS A laboratory test that separates molecules based on their size, shape, or electrical charge.

HEMOGLOBIN S Hemoglobin produced in association with the sickle cell trait; the beta-globin molecules of hemoglobin S are abnormal.

HEMOLYTIC Refers to the type of anemia caused by the breakdown of red blood cells, as opposed to anemia due to decreased production, for example.

HEMOLYTIC ANEMIA Anemia that results from premature destruction and decreased numbers of red blood cells.

HEMORRHAGE Very severe, massive bleeding that is difficult to control. Hemorrhage can occur in hemophiliacs after what would be a relatively minor injury to a person with normal clotting factors.

HEMOSTASIS The arrest of bleeding by blood coagulation.

HEPATIC Referring to the liver.

HEPATITIS A viral disease characterized by inflammation of the liver cells (hepatocytes). People infected with hepatitis B or hepatitis C virus are at an increased risk for developing liver cancer.

HEPATOMEGALY An abnormally large liver.

HEPATOSPLENOMEGALY Enlargement of the liver and spleen.

HEREDITARY ANGIONEUROTIC EDEMA Abbreviated HANE, or HAE, this is an inherited kind of angioneurotic edema. Type I HANE is caused by a deficiency of C1-INH. Type II HANE is caused by a malformation of the C1-INH protein.

HEREDITARY NON-POLYPOSIS COLON CANCER (HNPCC) A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called Lynch syndrome.

HERITABILITY The proportion of causative factors for a disease that can be attributed to genetics.

HERMANSKY-PUDLAK SYNDROME (HPS) A rare form of albinism, most common in the Puerto Rican community, which can cause pigment changes, lung disease, intestinal disorders, and blood disorders.

HERNIA A rupture in the wall of a body cavity, through which an organ may protrude.

HETEROCHROMIA IRIDES A medical term for individuals with different-colored eyes.

HETEROGENEOUS A set of symptoms or a disorder caused by several different gene mutations.

HETEROPLASMY When all copies of mitochondrial DNA are not the same, and a mix of normal and mutated mitochondrial DNA is present.

HETEROTOPIA Small nodules of gray matter that are present outside the cortex.

HETEROZYGOTE/HETEROZYGOUS Having two different versions of the same gene.

HIGH DENSITY LIPOPROTEIN (HDL) A cholesterol carrying substance that helps remove cholesterol from the cells of the body and deliver it to the liver where it is digested and removed from the body.

HIGH-FUNCTIONING AUTISM (HFA) A subcategory of autistic disorder consisting of children diagnosed with IQs of 70 or higher.

HIGHLY AEROBIC TISSUES Tissue that requires the greatest amount of oxygen to thrive.

HIRSCHPRUNG DISEASE A deformation in which the colon becomes enlarged (megacolon), caused by abnormal nerve control of that portion of the large intestine.

HIRSUITISM The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

HISTAMINE A substance released by immune system cells in response to the presence of an allergen; stimulates widening of blood vessels and increased porousness of blood vessel walls so that fluid and protein leaks out from blood to surrounding tissue, causing inflammation of local tissues.

HISTOLOGIC Pertaining to histology, the study of cells and tissues at the microscopic level.

HLA TYPE Refers to the unique set of proteins called human leukocyte antigens. These proteins are present on each individual's cell and allow the immune system to recognize 'self' from 'non-self'. HLA type is particularly important in organ and tissue transplantation.

HLA-B27 Stands for a specific form of human leukocyte antigen, the proteins involved in immune system function. Strongly associated with ankylosing spondylitis.

HMLH1 AND HMSH2 Genes known to control mismatch repair of genes.

HOLT-ORAM SYNDROME Inherited disorder characterized by congenital heart defects and abnormalities of the arms and hands; may be associated with Duane retraction syndrome.

HOMEOPATHIC A holistic and natural approach to health care.

HOMEOSTASIS A state of physiological balance.

HOMEOTIC GENES Developmental control genes active in the embryo.

HOMOCYSTEINE An amino acid that is not used to produce proteins in the human body.

HOMOGENTISATE 1,2-DIOXYGENASE (HGD) Homogentisic acid oxidase, the fourth enzyme in the metabolic pathway for the breakdown of phenylalanine.

HOMOGENTISIC ACID (HGA) 2,5-Dihydroxyphenylacetic acid, the third intermediate in the metabolic pathway for the breakdown of phenylalanine.

HOMOLOGOUS CHROMOSOMES Homologous chromosomes are two chromosomes of a doublet set that are identical, particularly for the genes that are on them.

HOMOLOGUES Chromosomes or chromosome parts identical with respect to their construction and genetic content (i.e. the two chromosome 1s are homologous, as are the two #2s, #3s, etc . . .).

HOMOPLASMY When all copies of mitochondrial DNA are the same, or have the same mutation.

HOMOZYGOTE/HOMOZYGOUS Having two identical copies of a gene or chromosome.

HORMONE A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

HORMONE THERAPY Treatment of cancer by changing the hormonal environment, such as testosterone and estrogen.

HUMAN GENOME PROJECT An international collaborative project among scientists to map the genetic sequence of all the chromosomes. This project is funded by the National Institute of Health in the United States.

HUMAN LEUKOCYTE ANTIGENS (HLA) Proteins that help the immune system function, in part by helping it to distinguish 'self' from 'non-self'.

HUMORAL IMMUNITY A type of acquired immunity mediated by B-cells and their secreted antibodies; important in fighting bacterial and some viral infections.

HUNTINGTON DISEASE A midlife-onset inherited disorder characterized by progressive dementia and loss of control over voluntary movements. It is sometimes called Huntington's chorea.

HUNTINGTON'S CHOREA A hereditary disease that typically appears in midlife, marked by gradual loss of brain function and voluntary movement. Some of its symptoms resemble those of schizophrenia.

HYALINE A clear substance that occurs in cell deterioration.

HYDRAMNIOS A condition in which there is too much amniotic fluid in the womb during pregnancy.

HYDROCEPHALUS The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

HYDROLASE Enzyme that uses water to break down substances.

HYDROMETROCOLPOS An abnormal accumulation of fluids in the uterus and vagina.

HYDRONEPHROSIS Obstruction of the tube that carries urine from the kidney into the bladder causing the pelvis and kidney duct to become swollen with excess urine.

HYDROPS FETALIS A condition characterized by massive edema in a fetus or newborn.

HYDROXYAPATITE A mineral that gives bone its rigid structure and strength. It is primarily composed of calcium and phosphate.

HYDROXYUREA A drug that has been shown to induce production of fetal hemoglobin. Fetal hemoglobin has a pair of gamma-globin molecules in place of the typical beta-globins of adult hemoglobin. Higher-than-normal levels of fetal hemoglobin can ameliorate some of the symptoms of thalassemia.

HYPERAMMONEMIA An excess of ammonia in the blood.

HYPERCALCEMIA High levels of calcium in the blood.

HYPEREXTENSIBILITY The ability to extend a joint beyond the normal range.

HYPERHIDROSIS Excessive perspiration that may be either general or localized to a specific area.

HYPERKERATOSIS Thickening of the skin.

HYPERLORDOSIS An exaggerated curve in the lower (lumbar) portion of the back.

HYPERMOBILITY Unusual flexibility of the joints, allowing them to be bent or moved beyond their normal range of motion.

HYPERPHAGIA Over-eating.

HYPERPIGMENTATION An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

HYPERSENSITIVE A process or reaction that occurs at above normal levels; overreaction to a stimulus.

HYPERTELORISM A wider-than-normal space between the eyes.

HYPERTHERMIA Body temperature that is much higher than normal (i.e. higher than 98.6°F).

HYPERTONIA Excessive muscle tone or tension, causing resistance of muscle to being stretched.

HYPERTRICHOSIS Growth of hair in excess of the normal. Also called hirsutism.

HYPERTROPHIC CARDIOMYOPATHY A condition in which the muscle of the heart is abnormally excessively thickened. In microscopic examination, normal alignment of muscle cells is absent (myocardial disarray).

HYPERTROPHY Increase in the size of a tissue or organ brought on by the enlargement of its cells rather than cell multiplication.

HYPNAGOGIC HALLUCINATIONS Dream-like auditory or visual hallucinations that occur while falling asleep.

HYPOCHONDROPLASIA An autosomal dominant form of dwarfism whose physical features are similar to those of achondroplasia but milder. Affected individuals have mild short stature and a normal facial appearance.

HYPOGLYCEMIA An abnormally low glucose (blood sugar) concentration in the blood.

HYPOGONADISM Small testes in men and scarce or irregular mentruation for females.

HYPOHIDROSIS Insufficient perspiration or absent perspiration which may be either general or localized to a specific area.

HYPOKETOSIS Decreased levels of ketone bodies.

HYPOMYELINATION The death of myelin on a nerve or nerves.

HYPOPHOSPHATEMIA The state of having abnormally low levels of phosphate in the bloodstream.

HYPOPIGMENTATION Decreased or absent color (pigment) in a tissue.

HYPOPLASIA/HYPOPLASTIC Incomplete or underdevelopment of a tissue or organ. Hypoplastic left heart syndrome is the most serious type of congenital heart disease.

HYPOSPADIAS An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

HYPOTHALAMUS A part of the forebrain that controls heartbeat, body temperature, thirst, hunger, body temperature and pressure, blood sugar levels, and other functions.

HYPOTHYROID Deficiency in thyroid gland activity or thyroid hormone levels.

HYPOTONIA Reduced or diminished muscle tone.

I

IATROGENIC Caused by (-genic) doctor (iatro-). An iatrogenic condition is a condition that is caused by the diagnosis or treatment administered by medical professionals. Iatrogenic conditions may be caused by any number of things, including: unsterile medical instruments or devices, contaminated blood or implantations, or contaminated air within the medical facility.

ICHTHYOSIS Rough, dry, scaly skin that forms as a result of an abnormality in skin formation.

IDIOPATHIC Of unknown origin.

IgE An antibody composed of protein; specific forms of IgE produced by cells of immune system in response to different antigens that contact the body; major factor that stimulates the allergic response.

ILIAC ARTERIES Arteries that supply blood to the lower body including the pelvis and legs.

IMMUNE SYSTEM A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

IMMUNODEFICIENCY A disorder in the immune system that leaves an individual vulnerable to infection.

IMMUNOGLOBULIN A protein molecule formed by mature B cells in response to foreign proteins in the body; the building blocks for antibodies.

IMMUNOLOGIC Related to immunology, the study of how the body's immune system fights disease. Many immunologic disorders are characterized by the body's use of antibodies.

IMMUNOTHERAPY Treatment of cancer by stimulating the body's immune defense system.

IMPAIRED GLUCOSE TOLERANCE (IGT) May be a precursor to diabetes; marked by blood glucose levels that are not quite elevated to the level seen in nephrogenic diabetes insipidus.

IMPERFORATE ANUS Also known as anal atresia. A birth defect in which the opening of the anus is absent or obstructed.

IMPOTENCE The inability to have a penile erection, which can be due to tissue damage resulting from sickling within the penis (priapism).

IMPRINTING Process that silences a gene or group of genes. The genes are silenced depending on if they are inherited through the egg or the sperm.

IN UTERO While in the uterus; before birth.

IN VITRO FERTILIZATION Process by which a woman has her eggs surgically removed and fertilized in the laboratory. The developing embryos can then be transferred to her uterus to hopefully achieve a pregnancy.

INCLUSION BODY Abnormal storage compartment inside a cell.

INDUCTION Process where one tissue (the prechordal plate, for example) changes another tissue (for example, changes tissue into neural tissue).

INFANTILE SPASMS The form of grand mal or focal seizures experienced by infants prior to the development of many voluntary muscular controls.

INFECTIVE ENDOCARDITIS An infection of the endothelium, the tissue lining the walls of the heart.

INFERTILITY Inability in a woman to become pregnant.

INFLAMMATION Swelling and reddening of tissue; usually caused by the immune system's response to the body's contact with an allergen.

INFORMED CONSENT Provision of complete information to a competent individual regarding a treatment or test. Part of informed consent is to ensure a patient's understanding of the pros and cons of a procedure and to get their voluntary authorization to perform the procedure.

INGUINAL HERNIA A condition in which part of the intestines protrudes through a tear in the muscles of the abdomen.

INHERITANCE PATTERN The way in which a genetic disease is passed on in a family.

INHERITED GIANT PLATELET DISORDER (IGPD) A group of hereditary conditions that cause abnormal blood clotting and other conditions.

INSOMNIA An inability to either fall or stay asleep, particularly at a time of day when sleep is expected. A number of medications are available and may be used for treatment.

INSULIN A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

INSULIN RECEPTOR GENE The gene responsible for the production of insulin receptor sites on cell surfaces. Without properly functioning insulin receptor sites, cells cannot attach insulin from the blood for cellular use.

INSULIN RESISTANCE An inability to respond normally to insulin in the bloodstream.

INSULIN-DEPENDENT DIABETES MELLITUS (IDDM) Synonymous with type I diabetes, the more serious form of diabetes that tends to affect people at a younger age.

INSULIN-LIKE GROWTH FACTOR I A hormone released by the liver in response to high levels of growth hormone in the blood. This growth factor is very similar to insulin in chemical composition; and, like insulin, it is able to cause cell growth by causing cells to undergo mitosis (cell division).

INTERPERSONAL THERAPIES Also called "talking therapy," this type of psychological counseling is focused on determining how dysfunctional interpersonal relationships of the affected individual may be causing or influencing symptoms of depression.

INTRACRANIAL HEMORRHAGE Abnormal bleeding within the space of the skull and brain.

INTRACRANIAL PRESSURE The pressure of the fluid between the brain and skull.

INTRAGENIC Occuring within a single gene.

INTRAUTERINE Situated or occurring in the uterus.

INTRAUTERINE GROWTH RETARDATION A form of growth retardation occurring in the womb that is not caused by premature birth or a shortened gestation time. Individuals affected with this condition are of lower than normal birth weight and lower than normal length after a complete gestation period.

INTRAVENOUS A route for administration of fluids, nutrients, blood products, or medications. A small, flexible plastic tube is inserted into a vein by way of a needle to establish this route.

INTRAVENOUS PYELOGRAM An x ray assessment of kidney function.

INTRON Portion of the DNA sequence of a gene that is not directly involved in the formation of the chemical that the gene codes for.

INTUSSUSCEPTION One piece of bowel inside another, causing obstruction.

INVERSION A type of chromosomal disorder in which a broken segment of a chromosome attaches to the same chromosome, but in reverse position.

ION CHANNEL Cell membrane proteins that control the movement of ions into and out of a cell.

IONIZING RADIATION High-energy radiation such as that produced by x rays.

IQ Abbreviation for Intelligence Quotient. Compares an individual's mental age to his/her true or chronological age and multiplies that ratio by 100.

IRIS The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

IRON OVERLOAD A side effect of frequent blood transfusions in which the body accumulates abnormally high levels of iron. Iron deposits can form in organs, particularly the heart, and cause life-threatening damage.

ISCHEMIC ATTACK A period of decreased or no blood flow.

ISCHOPAGUS Conjoined twins who are attached at the lower half of the body.

ISOMERISM Refers to the organs that typically come in pairs, but where the right organ is structurally different from the left organ. In a condition like asplenia, however, the organs are identical.

ISOMERS Two chemicals identical in chemical composition (contain the same atoms in the same amounts) that have differing structures. The normal prion protein and the infectious prion protein are conformational isomers of one another. They have the same chemical structures, but for some reason, assume different shapes.

ISOTOPE Any of two or more species of atoms of a chemical element with the same atomic number and nearly identical chemical behavior, but with differing atomic mass and physical properties.

ISOZYME/ISOENZYME A group of enzymes that perform the same function, but are different from one another in their structure or how they move.

J

JAUNDICE Yellowing of the skin or eyes due to an excess of bilirubin in the blood.

JOINT CONTRACTURES Stiffness of the joints that prevents full extension.

JOINT DISLOCATION The displacement of a bone from its socket or normal position.

K

KABUKI Traditional Japanese popular drama performed with highly stylized singing and dancing using special makeup and cultural clothing.

KALLIKREIN A protein necessary for the activation of chemicals that cause dilation of blood vessels to allow increased blood flow to an area that requires more blood than normal. It is also capable of cleaving the complement, C5, into C5a, a much more robust and active form of this complement molecule.

KANNER'S SYNDROME Another name for autism.

KARYOTYPE A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

KARYOTYPING A laboratory procedure in which chromosomes are separated from cells, stained, and arranged so that their structure can be studied under the microscope.

KERATIN A tough, non-water-soluble protein found in the nails, hair, and the outermost layer of skin. Human hair is made up largely of keratin.

KERATINOCYTES Skin cells.

KERATOACANTHOMA A firm nodule on the skin typically found in areas of sun exposure.

KERATOLYTIC An agent that dissolves or breaks down the outer layer of skin (keratins).

KERATOSIS A raised thickening of the outer horny layer of the skin.

KETOACIDOSIS A condition that results when organic compounds (such as propionic acid, ketones, and fatty acids) build up in the blood and urine.

KETOLACTIC ACIDOSIS The overproduction of ketones and lactic acid.

KETONE BODIES Products of fatty acid metabolism in the liver that can be used by the brain and muscles as an energy source.

KETONES "Fuel" molecules that can accumulate and cause the potentially life-threatening complication of ketosis.

KETONURIA The presence of excess ketone bodies (organic carbohydrate-related compounds) in the urine.

KETOSIS An abnormal build-up of chemicals called ketones in the blood. This condition usually indicates a problem with blood sugar regulation.

KIDNEY Either of two organs in the lumbar region that filter the blood, excreting the end products of the body's metabolism in the form of urine and regulating the concentrations of hydrogen, sodium, potassium, phosphate, and other ions in the body.

KIDNEY TUBULES A portion of the kidneys that causes water to be excreted as urine or reabsorbed into the body.

KLINEFELTER SYNDROME A syndrome that occurs in XXY males; characterized by sterility and small testes; normal intelligence.

KNOCKOUT EXPERIMENT A type of genetic experiment in which researchers are able to deactivate, or knock out, a gene that may influence a particular trait, such as vulnerability to alcohol.

KYPHOSCOLIOSIS Abnormal front-to-back and side-to-side curvature of the spine.

KYPHOSIS An abnormal outward curvature of the spine, with a hump at the upper back.

L

L-CARNITINE A substance made in the body that carries wastes from the body's cells into the urine.

LABIA Lips of the female genitals.

LACRIMAL DUCTS Tear ducts.

LACTIC ACID The major by-product of anaerobic (without oxygen) metabolism.

LACTIC ACIDOSIS A condition characterized by the accumulation of lactic acid in bodily tissues. The cells of the body make lactic acid when they use sugar as energy. If too much of this acid is produced, the person starts feeling ill with symptoms such as stomach pain, vomiting, and rapid breathing.

LACTOSE A sugar made up of of glucose and galactose. It is the primary sugar in milk.

LAPAROSCOPY A diagnostic procedure in which a small incision is made in the abdomen and a slender, hollow, lighted instrument is passed through it. The doctor can view the ovaries more closely through the laparoscope, and if necessary, obtain tissue samples for biopsy.

LAPAROTOMY An operation in which the abdominal cavity is opened up.

LARYNX The voice box, or organ that contains the vocal cords.

LASER-ASSISTED IN-SITU KERATOMILEUSIS (LASIK) A procedure that uses a cutting tool and a laser to modify the cornea and correct moderate to high levels of myopia.

LATERAL RECTUS MUSCLE The muscle that turns the eye outward toward the ear (abduction).

LEBERS HEREDITARY OPTIC ATROPHY OR LEBERS HEREDITARY OPTIC NEUROPATHY (LHON) Discovered in 1871 by Theodore Leber, the painless loss of central vision in both eyes, usually occurring in the second or third decade of life, caused by a mutation in mitochondrial DNA. Other neurological problems such as tremors or loss of ankle reflexes may also be present.

LEFT VENTRICULAR ENLARGEMENT Abnormal enlargement of the left lower chamber of the heart.

LENS The transparent, elastic, curved structure behind the iris (colored part of the eye) that helps focus light on the retina.

LENTIGENE A dark colored spot on the skin.

LEPROSY A chronic, contagious skin and nervous system disease that leads, in the more serious form, to numbness, muscle weakness, and paralysis. Leprosy is sometimes referred to as Hansen's disease.

LEPTOMENINGEAL ANGIOMA A swelling of the tissue or membrane surrounding the brain and spinal cord, which can enlarge with time.

LESION An abnormal or injured section or region of the brain (or other body organ).

LEUCOPENIA A decrease in white blood cells.

LEUKEMIA Cancer of the blood forming organs that results in an overproduction of white blood cells.

LEUKOCYTE A white blood cell. The neutrophils are a type of leukocyte.

LEUKOCYTOSIS An increase in the number of leukocytes in the blood.

LEUKODYSTROPHY A disease that affects the white matter called myelin in the CNS.

LEUKOENCEPHALOPATHY Any of various diseases, including leukodystrophies, affecting the brain's white matter.

LEVOTHYROXINE A form of thyroxine (T4) for replacement of thyroid hormones in hypothryoidism.

LEWY BODIES Areas of injury found on damaged nerve cells in certain parts of the brain associated with dementia.

LI-FRAUMENI SYNDROME Inherited syndrome known to cause increased risk of different cancers, most notably sarcomas.

LIFETIME RISK A risk that exists over a person's lifetime; a lifetime risk to develop disease means that the chance is present until the time of death.

LIGAMENT A type of connective tissue that connects bones or cartilage and provides support and strength to joints.

LIMB DYSTONIA Involuntary cramp or spasm that affects the hands. Also known as writer's cramp.

LIMB GIRDLES Areas around the shoulders and hips.

LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMD) Form of muscular dystrophy that begins in late childhood to early adulthood and affects both men and women, causing weakness in the muscles around the hips and shoulders.

LIMITED SCLERODERMA A subtype of systemic scleroderma with limited skin involvement. It is sometimes called the CREST form of scleroderma, after the initials of its five major symptoms.

LINKAGE The association between separate DNA sequences (genes) located on the same chromosome.

LINKAGE ANALYSIS A method of finding mutations based on their proximity to previously identified genetic landmarks.

LIPASE A digestive enzyme found in pancreatic fluid that breaks down fats.

LIPID Large, complex biomolecule, such as a fatty acid, that will not dissolve in water. A major constituent of membranes.

LIPOMA A benign tumor composed of well-differentiated fat cells.

LIPOPIGMENTS Substances made up of fats and proteins found in the body's tissues.

LIPOPROTEIN A lipid and protein chemically bound together, which aids in transfer of the lipid in and out of cells, across the wall of the intestine, and through the blood stream.

LIPOSOME Fat molecule made up of layers of lipids.

LISSENCEPHALY A condition in which the brain has a smooth appearance because the normal convolutions (gyri) failed to develop.

LOCALIZED SCLERODERMA Thickening of the skin from overproduction of collagen.

LOCI The physical location of a gene on a chromosome.

LONGITUDINAL STUDY A type of research project in which the same subjects are interviewed repeatedly at intervals over a period of time.

LORICIN One of the proteins that give skin cells their structure.

LOW DENSITY LIPOPROTEINS (LDL) A cholesterol carrying substance that can remain in the blood stream for a long period of time.

LUMBAR LORDOSIS Abnormal inward curvature of the spine.

LUPUS ERYTHEMATOSUS A chronic inflammatory disease that affects many tissues and parts of the body including the skin.

LUTENIZING HORMONE (LH) A hormone secreted by the pituitary gland that regulates the menstrual cycle and triggers ovulation in females. In males it stimulates the testes to produce testosterone.

LYMPH NODE A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

LYMPHATIC SYSTEM Lymph nodes and lympatic vessels that transport infection fighting cells to the body.

LYMPHEDEMA DISTICHIASIS Autosomal dominant condition with abnormal or absent lymph vessels. Common signs include a double row of eyelashes (distichiasis) and edema of the limbs beginning around puberty.

LYMPHOCYTES Also called white blood cells, lymphocytes mature in the bone marrow to form B cells, which fight infection.

LYMPHOMA A malignant tumor of the lymph nodes.

LYNCH SYNDROME A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called hereditary non-polyposis colon cancer (HNPCC).

LYSINE A crystalline basic amino acid essential to nutrition.

LYSIS Area of destruction.

LYSOSOMAL Pertaining to the lysosomes, special parts (organelles) of cells that contain a number of enzymes important in the breakdown of large molecules such as proteins and fats.

LYSOSOMAL STORAGE DISEASE A category of disorders that includes mannosidosis.

LYSOSOME Membrane-enclosed compartment in cells containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

M

MACROCEPHALY A head that is larger than normal.

MACROGLOSSIA A large tongue.

MACROMOLECULES A large molecule composed of thousands of atoms.

MACROPHAGE Specialized white blood cells that play a role in breaking down old or abnormal red blood cells.

MACROSOMIA Overall large size due to overgrowth.

MACROSTOMIA A mouth that is larger or wider than normal.

MACULA A small spot located in the back of the eye that provides central vision and allows people to see colors and fine visual details.

MACULE A flat, discolored spot or patch on the skin.

MADAROSIS The medical term for loss of hair from the eyebrows or eyelashes. Madarosis may be associated with a form of alopecia areata called alopecia totalis. It may also result from such diseases as leprosy and syphilis, or from trauma.

MADELUNG'S DEFORMITY A forearm bone malformation characterized by a short forearm, arched or bow shaped radius, and dislocation of the ulna.

MAFFUCCI DISEASE A manifestation of Ollier disease (multiple enchondromatosis) with hemangiomas, which present as soft tissue masses.

MAGNETIC RESONANCE IMAGING (MRI) A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

MAJOR DEPRESSION A psychological condition in which the patient experiences one or more disabling attacks of depression that lasts two or more weeks.

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) Includes HLA, as well as other components of the immune system. Helps the immune system function, in part by helping it to distinguish 'self' from 'non-self'.

MALAR HYPOLPLASIA Small or underdeveloped cheekbones.

MALE-LETHAL X-LINKED DOMINANCE An inheritance pattern in which affected male children die from the characteristics of the trait. This death is typically either embryonic, fetal, or neonatal.

MALIGNANT A tumor growth that spreads to another part of the body; usually cancerous.

MALIGNANT HYPERTHERMIA A condition brought on by anesthesia during surgery.

MALROTATION An abnormality that occurs during the normal rotation of an organ or organ system.

MAMMOGRAM A procedure in which both breasts are compressed/flattened and exposed to low doses of x rays, in an attempt to visualize the inner breast tissue.

MAMMOGRAPHY X rays of the breasts; used to screen for breast cancer.

MANDIBLE Lower jaw bone.

MANDIBULAR HYPOPLASIA Underdevelopment of the lower jaw.

MANNOSE A type of sugar that forms long chains in the body.

MANOMETRY A balloon study of internal anal sphincter pressure and relaxation.

MAO-B INHIBITORS Inhibitors of the enzyme monoamine oxidase B. MAO-B helps break down dopamine; inhibiting it prolongs the action of dopamine in the brain. Selegiline is an MAO-B inhibitor.

MAORI A native New Zealand ethnic group.

MARFANOID Term for body type that is similar to people with Marfan syndrome. Characterized by a tall, lean body with long arms and long fingers.

MARFANOID HABITUS An abnormally low weight to height ratio that is sometimes seen in extremely tall and thin people.

MASCULINIZATION Development of excess body and facial hair, deepening of the voice, and increase in muscle bulk in a female due to a hormone disorder.

MASSETER SPASM Stiffening of the jaw muscles. Often one of the first symptoms of malignant hyperthermia susceptibility that occurs after exposure to a trigger drug.

MATERNAL Relating to the mother.

MATERNAL SERUM SCREENING A blood test offered to pregnant women usually under the age of 35, which measures analytes in the mother's blood that are present only during pregnancy, to screen for Down syndrome, trisomy 18, and neural tube disorders.

MATERNAL UNIPARENTAL DISOMY Chromosome abnormality in which both chromosomes in a pair are inherited from the mother.

MATURITY-ONSET DIABETES OF THE YOUNG (MODY) A dominantly-inherited subtype of NIDDM with clear genetic inheritance. Onset tends to be earlier than in NIDDM.

MAXIALLARY HYPOPLASIA Underdevelopment of the upper jaw.

MAXILLA One of the bones of the face.

MECONIUM The first waste products to be discharged from the body in a newborn infant, usually greenish in color and consisting of mucus, bile, and so forth.

MEDIAL RECTUS MUSCLE The muscle that turns the eye inward toward the nose (adduction).

MEDIUM CHAIN ACYL-COA DEHYDROGENASE Abbreviated MCAD, this is the enzyme responsible for the breakdown of medium chain fatty acids in humans. People affected with MCAD deficiency produce a form of MCAD that is not as efficient as the normal form of MCAD.

MEDIUM CHAIN FATTY ACIDS Fatty acids containing between four and 14 carbon atoms.

MEDULLARY CAVITY The marrow-filled cavity inside of a long bone (such as the femur).

MEDULLOBLASTOMA Tumor of the central nervous system derived from undifferentiated cells of the primitive medullary tube.

MEGACOLON Dilation of the colon.

MEIOSIS The process in which a cell in the testes or ovaries undergoes chromosome separation and cell division to produce sperm or eggs.

MELANIN Pigments normally produced by the body that give color to the skin and hair.

MELANOCYTES A cell that can produce melanin.

MELANOMA Tumor, usually of the skin.

MELANOSOMES Granules of pigment within melanocytes that synthesize melanin.

MELATONIN A sleep-inducing hormone secreted by the pineal gland.

MEMORY CELLS B-cells whose antibodies recognized antigens from a previous infection; able to mount a quick, efficient response upon a second infection by the same organism.

MENDEL, GREGOR Austrian monk who discovered the basic principals of heredity.

MENINGES The two-layered membrane that covers the brain and spinal cord.

MENINGITIS An infection of the covering of the brain.

MENOPAUSE Cessation of menstruation in the human female, usually occurring between the ages of 46 and 50.

MENSTRUATION Discharge of blood and fragments of the uterine wall from the vagina in a monthly cycle in the absence of pregnancy.

MENTAL RETARDATION Significant impairment in intellectual function and adaptation in society. Usually associated with an intelligence quotient (IQ) below 70.

MERMAID SYNDROME Alternate name for sirenomelia, often used in older references.

MESOMELIA Shortness of the portion of arm connecting the elbow to the wrist or forearm.

MESOMELIC The anatomical term used to describe the middle of a limb. The bones that constitute the middle of the arm are the radius and ulna, and mesomelic bones of the leg are the tibia and fibula.

METABOLIC ACIDOSIS High acidity (low pH) in the body due to abnormal metabolism, excessive acid intake, or retention in the kidneys.

METABOLIC DISORDER A disorder that affects the metabolism of the body.

METABOLIC MYOPATHIES A broad group of muscle diseases whose cause is a metabolic disturbance of some type.

METABOLIC PATHWAY A sequence of chemical reactions that lead from some precursor to a product, where the product of each step in the series is the starting material for the next step.

METABOLISM The total combination of all of the chemical processes that occur within cells and tissues of a living body.

METACARPAL A hand bone extending from the wrist to a finger or thumb.

METACENTRIC When a chromosome has the centromere in the middle of the chromosome it is called a metacentric chromosome.

METACHRONOUS Occurring at separate time intervals.

METAFEMALE An out of date term for XXX females; also called triple X syndrome.

METAPHYSEAL FLARING A characteristic found only by x rays. If present, it means that the ends of the bone are wider than normal.

METAPHYSES The growth zone of the long bones located between the ends (epiphyses) and the shaft (diaphysis) of the bone.

METAPHYSIS An area of softer bone and cartilage in long bones between the diaphysis (shaft) and epiphysis (end).

METASTASIS The spreading of cancer from the original site to other locations in the body.

METASTATIC CANCER A cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.

METATARSAL A foot bone extending from the ankle to a toe.

METHYLATION TESTING DNA testing that detects if a gene is active or if it is imprinted.

METHYLMALONIC ACID An intermediate product formed when certain substances are broken down in order to create usable energy for the body.

METHYLMALONIC COA MUTASE (MCM) The enzyme responsible for converting methylmalonic acid to succinic acid, in the pathway to convert certain substances to usable energy.

METHYLMALONICACIDEMIA The build-up of high levels of methylmalonic acid in the bloodstream due to an inborn abnormality in an enzyme.

METHYLMALONICACIDURIA The buildup of high levels of methylmalonic acid in the urine due to an inborn defect in an enzyme.

MICRO-DELETION SYNDROME A collection of signs and symptoms caused by a deletion of a gene or genes that is too small to be seen through the microscope.

MICROARRAY An ordered arrangement of many different genes on a glass slide or silicon chip. Microarrays allow researchers to study large numbers of genes simultaneously in determining different levels of gene activity in such complex processes as the body's response to alcohol.

MICROCEPHALIC Having an abnormally small head.

MICROCEPHALIC PRIMORDIAL DWARFISM SYNDROMES A group of disorders characterized by profound growth delay and small head size.

MICROCEPHALY An abnormally small head.

MICROCORNEA Abnormal smallness of the cornea.

MICRODONTIA Small teeth.

MICROGNATHIA A term used to describe small, underdeveloped lower jaw and chin.

MICROGNATHY Having a very small and receding jaw.

MICROMELIA The state of having extremely short limbs.

MICROPHTHALMIA Small or underdeveloped eyes.

MICROTIA Small or underdeveloped ears.

MIDLINE DEFECTS Disorders involving organs along the center of the body such as the lips, penis, and corpus callosum.

MIDLINE ORGANS Organs found along the center of the body such as the lips, penis, and corpus callosum.

MINIATURIZATION The process of shortening and thinning of the hair shafts that is found in androgenetic alopecia. It is caused by the effects of DHT on the hair follicle.

MINOXIDIL A topical medication sold under the trade name Rogaine for the treatment of male pattern hair loss. It is applied to the scalp as a 2% or 5% solution.

MISCARRIAGE Spontaneous pregnancy loss.

MISMATCH REPAIR Repair of gene alterations due to mismatching.

MITOCHONDRIA Organelles within the cell responsible for energy production.

MITOCHONDRIAL INHERITANCE Inheritance associated with the mitochondrial genome, which is inherited exclusively from the mother.

MITOCHONDRIAL MYOPATHIES Diseases of the muscle accompanied by abnormal changes in the cell mitochondria that results in excessive accumulation of lipids.

MITOSIS The process by which a somatic cell—a cell not destined to become a sperm or egg—duplicates its chromosomes and divides to produce two new cells.

MITRAL VALVE The heart valve that prevents blood from flowing backwards from the left ventricle into the left atrium. Also known as bicuspid valve.

MITRAL VALVE PROLAPSE A heart abnormality in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur but there are usually no symptoms.

MIXED TYPE HEARING LOSS Hearing loss that involves both conductive and sensorineural losses.

MONOSOMY Missing an entire copy of a chromosome or a piece of one copy of a chromosome.

MONOZYGOTIC From one zygote, as in identical twins. The zygote is the first cell formed by the union of sperm and egg.

MORPHEA The most common form of localized scleroderma.

MOSAIC A term referring to a genetic situation in which an individual's cells do not have the exact same composition of chromosomes. In Down syndrome, this may mean that some of the individual's cells have a normal 46 chromosomes, while other cells have an abnormal 47 chromosomes.

MOSAICISM A genetic condition resulting from a mutation, crossing over, or nondisjunction of chromosomes during cell division, causing a variation in the number of chromosomes in the cells.

MOTOR FUNCTION The ability to produce body movement by complex interaction of the brain, nerves, and muscles.

MOTOR NEURONS Class of neurons that specifically control and stimulate voluntary muscles.

MOTOR SKILLS DISORDER A disorder that affects motor coordination or its development, and the control of particular groups of muscles that perform activities.

MOTOR UNITS Functional connection with a single motor neuron and muscle.

MOTTLED RETINA Changes in the retina of the eye causing a loss of visual acuity.

MUCOCILIARY ESCALATOR The coordinated action of tiny projections on the surfaces of cells lining the respiratory tract, which moves mucus up and out of the lungs.

MUCOLIPID Lipid that accumulates in cells in mucolipidosis disorders.

MUCOLIPIN-1 Protein in the cell membrane, probably a calcium ion channel, involved in recycling membrane lipids and is deficient in mucolipidosis IV.

MUCOLYTIC An agent that dissolves or destroys mucin, the chief component of mucus.

MUCOPOLYSACCHARIDE A complex molecule made of smaller sugar molecules strung together to form a chain. Found in mucous secretions and intercellular spaces.

MUCOPOLYSACCHARIDOSIS I H (MPS I H) Another name for Hurler syndrome.

MUCORMYCOSIS An organism that commonly infects individuals with diabetes following ketosis events.

MUCOUS MEMBRANE Thin, mucous covered layer of tissue that lines organs such as the intestinal tract.

MULLERIAN DUCTS Structures in the embryo that develop into the fallopian tubes, the uterus, the cervix, and the upper vagina in females.

MULTI-INFARCT DEMENTIA Dementia caused by damage to brain tissue resulting from a series of blood clots or clogs in the blood vessels. It is also called vascular dementia.

MULTIFACTORIAL Describes a disease that is the product of the interaction of multiple genetic and environmental factors.

MULTIFACTORIAL INHERITANCE A type of inheritance pattern where many factors, both genetic and environmental, contribute to the cause.

MULTIFOCAL BREAST CANCER Multiple primary cancers in the same breast.

MULTIPLE CARBOXYLASE DEFICIENCY A type of propionic acidemia characterized by an inability to metabolize biotin.

MULTIPLE SCLEROSIS (MS) A progressive degeneration of nerve cells that causes episodes of muscle weakness, dizziness, and visual disturbances, followed by periods of remission.

MURMUR A noise, heard with the aid of a stethoscope, made by abnormal patterns of blood flow within the heart or blood vessels.

MUSCULAR DYSTROPHY A group of inherited diseases characterized by progressive wasting of the muscles.

MUTAGEN An environmental influence that causes changes in DNA.

MUTANT A change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease.

MUTATION A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

MYELIN A fatty sheath surrounding nerves in the peripheral nervous system, which help them conduct impulses more quickly.

MYELODYSPLASIA A bone marrow disorder that can develop into aplastic anemia requiring bone marrow or stem cell transplantation.

MYELOMENINGOCELE A sac that protrudes through an abnormal opening in the spinal column.

MYOCLONUS Twitching or spasms of a muscle or an interrelated group of muscles.

MYOGLOBINURIA The abnormal presence of myoglobin, a product of muscle disintegration, in the urine. Results in dark-colored urine.

MYOPATHY Any abnormal condition or disease of the muscle.

MYOPIA Nearsightedness. Difficulty seeing objects that are far away.

MYOTONIA The inability to normally relax a muscle after contracting or tightening it.

MYOTONIC DYSTROPHY A form of muscular dystrophy, also known as Steinert's condition, characterized by delay in the ability to relax muscles after forceful contraction, wasting of muscles, as well as other abnormalities.

MYXEDEMA Swelling of the face, hands, feet, and genitals due to hypothyroidism.

MYXOID Resembling mucus.

N

N-ACETYLGLUCOSAMINE-1-PHOSPHOTRANSFERASE (GNPTA) Enzyme that attaches a signal to other enzymes and directs those enzymes to the lysosome; deficient in mucolipidoses II and III.

NALTREXONE A medication originally developed to treat addiction to heroin or morphine that is also used to treat alcoholism. It works by reducing the craving for alcohol rather than by producing vomiting or other unpleasant reactions.

NANISM Short stature.

NARCOTICS Strong, prescription medication that can be effective in treating pain, but has the potential to be habit-forming if their use is not supervised correctly.

NASOGASTRIC TUBE A long flexible tube inserted through the nasal passageways, down the throat, and into the stomach. Used to drain the contents of the stomach.

NATURAL IMMUNITY First line immune response that is non-specific. Includes action of phagocytes, natural killer cells, and complement cells.

NATURAL KILLER CELLS Specialized white blood cells involved in natural immunity. Can kill some viruses and cancer cells.

NECROSIS Death of a portion of tissue differentially affected by disease or injury.

NECROTIZING ENCEPHALOMYELOPATHY A progressive degeneration of the brain and central nervous system. This condition is fatal in nearly all individuals affected with type A pyruvate carboxylase deficiency.

NEGATIVE SYMPTOMS Symptoms of schizophrenia characterized by the absence or elimination of certain behaviors. DSM-IV specifies three negative symptoms: affective flattening, poverty of speech, and loss of will or initiative.

NEONATAL Neonatal refers to the first 28 days after birth.

NEONATOLOGIST A physician (pediatrician) who has special training in the care of newborns (neonates).

NEPHRONS Microscopic-size tubes that filter the water that flows into the kidneys.

NEPHROPATHY Kidney disease.

NEPHROSIS A non-inflammatory disease of the kidneys.

NERVE CONDUCTION TESTING Procedure that measures the speed at which impulses move through the nerves.

NERVOUS SYSTEM The complete network of nerves, sense organs, and brain in the body.

NEUCHAL TRANSLUCENCY A pocket of fluid at the back of an embryo's neck visible via ultrasound that, when thickened, may indicate the infant will be born with a congenital heart defect.

NEURAL Regarding any tissue with nerves, including the brain, the spinal cord, and other nerves.

NEURAL CREST CELLS A group of cells in the early embryo, located on either side of the area that will eventually develop into the spinal cord. The cells migrate (move) away from the area and give rise to various body structures, including melanocytes (pigment producing cells), certain structures of the face and head, and parts of the nervous system.

NEURAL TUBE DEFECT A group of severe birth disorders in which the brain and spinal cord are malformed and lack the protective skeletal and soft tissue encasement.

NEUROCRISTOPATHY A disorder that results from abnormal development and/or migration of the neural crest cells in the embryo.

NEURODEGENERATIVE Relating to degeneration of nerve tissues.

NEUROFIBROMA A soft tumor usually located on a nerve.

NEUROFIBROMATOSIS Progressive genetic condition often including multiple café-au-lait spots, multiple raised nodules on the skin known as neurofibromas, developmental delays, slightly larger head sizes, and freckling of the armpits, groin area, and iris.

NEUROLEPTIC Another name for the older type of antipsychotic medications given to schizophrenic patients.

NEUROLOGIC Relating to the brain and central nervous system.

NEUROLOGIST A physician who specializes in disorders of the nervous system, including the brain, spine, and nerves.

NEUROMETABOLIC DISORDER Any disorder or condition that affects both the central nervous system (CNS) and the metabolism of the body.

NEUROMUSCULAR Involving both the muscles and the nerves that control them.

NEUROMUSCULAR JUNCTION The site at which nerve impulses are transmitted to muscles.

NEURON The fundamental nerve cell that conducts impulses across the cell membrane.

NEURONAL CEROID LIPOFUSCINOSES A family of four progressive neurological disorders.

NEUROPATHY A condition caused by nerve damage. Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

NEUROTRANSMITTER Chemical in the brain that transmits information from one nerve cell to another.

NEUTROPENIA A condition in which the number of leukocytes (a type of white or colorless blood cell) is abnormally low, mainly in neutrophils (a type of blood cell).

NEUTROPHIL The primary type of white blood cell involved in inflammation. Neutrophils are a type of granulocyte, also known as a polymorphonuclear leukocyte.

NEVI Plural of nevus.

NEVUS Any anomaly of the skin present at birth, including moles and various types of birthmarks.

NEVUS FLAMMEUS A flat blood vessel tumor present at birth; also known as a "port wine stain."

NEWBORN SCREENING The act of testing all infants for a specific disease shortly after birth for the purpose of preventing disease progression through prompt medical treatment.

NITRATES/NITRITES Chemical compounds found in certain foods and water that, when consumed, may increase the risk of gastric cancer.

NITROGEN A gaseous element that makes up the base pairs in DNA.

NON-INSULIN-DEPENDENT DIABETES MELLITUS (NIDDM) Synonymous with type II diabetes, the most common form of diabetes that tends to be highly influenced by lifestyle factors and typically occurs in adulthood.

NON-SYNDROMIC HEARING LOSS Hearing loss that is not accompanied by other symptoms characteristic of a larger genetic syndrome.

NONDISJUNCTION Non-separation of a chromosome pair, during either meiosis or mitosis.

NONSPHEROCYTIC Literally means not sphere-shaped. Refers to the shape of red blood cells in non-spherocytic hemolytic anemia.

NONVERBAL LEARNING DISABILITY (NLD) A learning disability syndrome identified in 1989 that may overlap with some of the symptoms of Asperger syndrome.

NOONAN SYNDROME A genetic syndrome that possesses some characteristics similar to cardiofaciocutaneous syndrome. It is unclear whether the two syndromes are different or two manifestations of the same disorder.

NUCLEAR INHERITANCE Inheritance associated with the nuclear genome (the 23 pairs of chromosomes). This inheritance follows the rules of segregation developed by Gregor Mendel and is alternately termed Mendelian inheritance.

NUCLEIC ACID A type of chemical used as a component for building DNA. The nucleic acids found in DNA are adenine, thymine, guanine, and cytosine.

NUCLEOTIDES Building blocks of genes, which are arranged in specific order and quantity.

NUCLEUS The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

NYSTAGMUS Involuntary, rhythmic movement of the eye.

O

OBLIGATE CARRIER An individual who, based on pedigree analysis, must carry a genetic mutation for a particular genetic disease. Parents of a child with an autosomal recessive disorder are obligate carriers.

OBSESSIVE COMPULSIVE DISORDER (OCD) Disorder characterized by persistent, intrusive, and senseless thoughts (obsessions) or compulsions to perform repetitive behaviors that interfere with normal functioning.

OCCIPITAL LOBE An anatomical subdivision, located at the back of the brain, that contains the visual cortex.

OCHRONOSIS A condition marked by pigment deposits in cartilage, ligaments, and tendons.

OCULAR A broad term that refers to structure and function of the eye.

OCULAR ALBINISM A type of albinism that affects the vision.

OCULO Related to the eye.

OCULO-DIGITAL REFLEX A reflex causing an individual to press on their eyes with their fingers or fists.

OCULOCUTANEOUS ALBINISM Inherited loss of pigment in the skin, eyes, and hair.

OCULOMOTOR NERVE Cranial nerve III; the nerve that extends from the midbrain to several of the muscles that control eye movement.

OCULOPHARYNGEAL MUSCULAR DYSTROPHY (OPMD) Form of muscular dystrophy affecting adults of both sexes and causing weakness in the eye muscles and throat.

OKIHIRO SYNDROME Inherited disorder characterized by abnormalities of the hands and arms and hearing loss; may be associated with Duane retraction syndrome.

OLIGODACTYLY The absence of one or more fingers or toes.

OLIGODONITA The absence of one or more teeth.

OLIGOHYDRAMNIOS Reduced amount of amniotic fluid. Causes include non-functioning kidneys and premature rupture of membranes. Without amniotic fluid to breathe, a baby will have underdeveloped and immature lungs.

OLIGOSACCHARIDE Several monosaccharide (sugar) groups joined by glycosidic bonds.

OLLIER DISEASE Also termed multiple enchondromatosis. Excessive cartilage growth within the bone extremities that result in benign cartilaginous tumors arising in the bone cavity.

OMPHALOCELE A birth defect where the bowel and sometimes the liver, protrudes through an opening in the baby's abdomen near the umbilical cord.

OMPHALOPAGUS Conjoined twins who are attached at the abdomen.

ONYCHOGRYPHOSIS Overgrowth of the fingernails and toenails.

OPHTHALMOLOGIST A physician specializing in the medical and surgical treatment of eye disorders.

OPHTHALMOLOGY The medical specialty of vision and the eye.

OPHTHALMOSCOPE An instrument, with special lighting, designed to view structures in the back of the eye.

OPISTHOTONOS An arched position of the body in which only the head and feet touch the floor or bed when the patient is lying on their back.

OPTIC DISC The region where the optic nerve joins the eye, also refered to as the blind spot.

OPTIC NERVE A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

OPTOMETRIST A medical professional who examines and tests the eyes for disease and treats visual disorders by prescribing corrective lenses and/or vision therapy. In many states, optometrists are licensed to use diagnostic and therapeutic drugs to treat certain ocular diseases.

ORAL LOADING TEST A procedure in which cystine is administered orally to a patient and plasma levels of cystine are measured. Under normal circumstances, amino acids are absorbed by the intestine and result in an increase in plasma amino acid levels. However, in cystinuria, there is a problem in the absorption process and blood levels of amino acids do not rise or rise slowly after eating.

ORBITAL CYSTS Small fluid-filled sacs that abnormally develop inside the bony cavity of the skull that holds the eyeball.

ORGANELLE Small, sub-cellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

ORGANIC ACIDURIA The condition of having organic acid in the urine.

ORTHODONTIST Dentist who specializes in the correction of misaligned teeth.

ORTHOKERATOLOGY A method of reshaping the cornea using a contact lens. It is not considered a permanent method to reduce myopia.

ORTHOPEDIST A doctor specializing in treatment of the skeletal system and its associated muscles and joints.

ORTHOSTATIC HYPOTENSION A sudden decrease in blood pressure upon sitting up or standing. May be a side effect of several types of drugs.

OSMOLARITY The concentration of an osmotic solution, especially when measured in osmols or milliosmols per liter of solution.

OSMOTICALLY Referring to the movement of a solvent through a semipermeable membrane (as of a living cell) into a solution of higher solute concentration that tends to equalize the concentrations of solute on the two sides of the membrane.

OSSICLES Any of the three bones of the middle ear, including the malleus, incus, and stapes.

OSSIFICATION The process of the formation of bone from its precursor, a cartilage matrix.

OSTEOARTHRITIS A degenerative joint disease that causes pain and stiffness.

OSTEOCHONDROMATOSIS Another name for hereditary multiple exostoses, meaning a growth of bone and cartilage.

OSTEOMA A benign bone tumor.

OSTEOMALACIA The adult form of rickets, a lack of proper mineralization of bone.

OSTEOPENIA Abnormal bone mineralization, usually resulting from a failure of the rate of bone matrix formation to compensate for the rate of bone decomposition.

OSTEOPENIC Bone density that is somewhat low, but not osteoporotic.

OSTEOPOROSIS Loss of bone density that can increase the risk of fractures.

OTITIS MEDIA Inflammation of the middle ear, often due to fluid accumulation secondary to an infection.

OTOLARYNGOLOGIST Physician who specializes in the care of the ear, nose, and throat and their associated structures.

OTOSCLEROSIS The main type of non-syndromic progressive conductive hearing loss seen in humans. In very advanced cases, otosclerosis can become of mixed type.

OVA Another name for the egg cells that are located in the ovaries.

OVARY The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

OVULATION The monthly process by which an ovarian follicle or cyst ruptures, releasing a mature egg cell.

OXYGENATED BLOOD Blood carrying oxygen through the body.

OXYTOCIN A hormone that stimulates the uterus to contract during child birth and the breasts to release milk.

P

PACHYDERMA An abnormal skin condition in which excess skin is produced that appears similar to that of an elephant (pachyderm).

PACHYGYRIA The presence of a few broad gyri (folds) and shallow sulci (grooves) in the cerebral cortex.

PALATE The roof of the mouth.

PALLIATIVE Treatment done for relief of symptoms rather than a cure.

PALMOPLANTAR KERATODERMA Group of mostly hereditary disorders characterized by thickening of the corneous layer of skin (hyperkeratosis) on the palms and soles as a result of excessive keratin formation (protein in the skin, hair, and nails).

PALMOPLANTAR KERATOSIS A raised thickening of the outer horney layer of the skin on the palms of the hand and the soles of the feet.

PALPEBRAL FISSURES The opening between the upper and lower eyelids.

PALPITATION An irregular heartbeat.

PALSY Uncontrollable tremors.

PANCREAS An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

PANCREATIC INSUFFICIENCY Reduction or absence of pancreatic secretions into the digestive system due to scarring and blockage of the pancreatic duct.

PANCREATIC ISLET CELL Cells located in the pancreas that serve to make certain types of hormones.

PANCREATITIS Inflammation of the pancreas.

PANCYTOPENIA An abnormal reduction in the number of erythrocytes (red blood cells), leukocytes (a type of white or colorless blood cell), and blood platelets (a type of cell that aids in blood clotting) in the blood.

PANHYPOPITUITARISM Generalized decrease of all of the anterior pituitary hormones.

PAPILLOMA Any benign localized growth of the skin and the linings of the respiratory and digestive tracts. The most common papilloma is the wart.

PAPILLOMATOUS PAPULES Skin-colored, raised bumps (not warts) found on the skin. Most of these growths are benign (non-cancerous) and rarely become malignant (cancerous).

PARAPAGUS Conjoined twins who are joined at the side of their lower bodies.

PARAPLEGIA Loss of voluntary movement and sensation of both lower extremities.

PARASITIC TWINS Occurs when one smaller, malformed twin is dependent on the larger, stronger twin for survival.

PARASYMPATHETIC GANGLION CELL Type of nerve cell normally found in the wall of the colon.

PARATHYROID GLANDS A pair of glands adjacent to the thyroid gland that primarily regulate blood calcium levels.

PARESTHESIA An abnormal sensation resembling burning, pricking, tickling, or tingling.

PARKINSON DISEASE A disease of the nervous system most common in people over 60, characterized by a shuffling gait, trembling of the fingers and hands, and muscle stiffness. It may be related in some way to Lewy body dementia.

PARKINSONISM A set of symptoms originally associated with Parkinson disease that can occur as side effects of neuroleptic medications. The symptoms include trembling of the fingers or hands, a shuffling gait, and tight or rigid muscles.

PATAU SYNDROME A syndrome caused by trisomy 13; characterized by cleft palate, severe mental retardation, and many other physical abnormalities; usually lethal by age one.

PATELLA The kneecap.

PATERNAL Relating to one's father.

PATHOLOGIST A physician who specializes in the diagnosis of disease by looking at living tissues with a microscope.

PECTORALIS MUSCLES Major muscles of the chest wall.

PECTUS CARINATUM An abnormality of the chest in which the sternum (breastbone) is pushed outward. It is sometimes called "pigeon breast."

PECTUS EXCAVATUM An abnormality of the chest in which the sternum (breastbone) sinks inward; sometimes called "funnel chest."

PEDIGREE ANALYSIS Analysis of a family tree, or pedigree, in an attempt to identify the possible inheritance pattern of a trait seen in this family.

PELVIC EXAMINATION Physical examination performed by a physician, often associated with a Pap smear. The physician inserts his/her finger into a woman's vagina, attempting to feel the ovaries directly.

PENDRIN A protein encoded by the PDS (Pendred syndrome) gene located on chromosome 7q31. Pendrin protein is believed to transport iodide and chloride within the thyroid and the inner ear.

PENETRANCE The degree to which individuals possessing a particular genetic mutation express the trait that this mutation causes. One hundred percent penetrance is expected to be observed in truly dominant traits.

PEPTIC ULCER A wound in the bowel that can be caused by stomach acid or a bacterium called *Helicobacter pylori.*

PEPTIDE A molecular compound made of two or more amino acids.

PERCHLORATE DISCHARGE TEST A test used to check for Pendred syndrome by measuring the amount of iodine stored inside the thyroid gland. Individuals with Pendred syndrome usually have more iodine stored than normal, and thus their thyroid will release a large amount of iodine into the bloodstream when they are exposed to a chemical called perchlorate.

PERICARDIAL CAVITY Space occupied by the heart.

PERICARDITIS Inflammation of the pericardium, the membrane surrounding the heart.

PERINATOLOGIST A physician (obstetrician) who has special training in managing difficult pregnancies. Some prenatal tests, such as chorionic villus sampling and level II ultrasound, are performed primarily by perinatologists.

PERIOD OF SUSCEPTIBILITY The time when teratogens can cause harm to the developing fetus.

PERIODONTITIS Inflammatory reaction of the tissues surrounding and supporting the teeth that can progress to bone destruction and abscess formation, and eventual tooth loss.

PERIOSTEAL Relating to the periosteum, which is the connective tissue that covers all human bones.

PERIPHERAL NERVES Nerves throughout the body that carry information to and from the spinal cord.

PERIPHERAL NEUROPATHY Any disease of the nerves outside of the spinal cord, usually resulting in weakness and/or numbness.

PERIPHERAL VISION The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

PERITONITIS Inflammation of the peritoneum, the membrane surrounding the abdominal contents.

PERNICIOUS ANEMIA A blood condition with decreased numbers of red blood cells related to poor vitamin B_{12} absorption.

PEROXISOME A cellular organelle containing different enzymes responsible for the breakdown of waste or other products.

PERVASIVE DEVELOPMENTAL DISORDER (PDD) The term used by the American Psychiatric Association for individuals who meet some but not all of the criteria for autism.

PES PLANUS Flat feet.

PEUTZ-JEGHERS SYNDROME Inherited syndrome causing polyps of the digestive tract and spots on the mouth as well as increased risk of cancer.

PHAGOCYTE White blood cells capable of engulfing and destroying foreign antigen or organisms in the fluids of the body.

PHALANGES Long bones of the fingers and toes divided by cartilage around the knuckles.

PHALILALIA Involuntary echoing of the last word, phrase, sentence, or sound vocalized by oneself.

PHENOTYPE The physical expression of an individuals genes.

PHENYLALANINE An essential amino acid that must be obtained from food since the human body cannot manufacture it.

PHENYLKETORNURIA (PKU) An inborn error of metabolism that causes build-up of the amino acid, phenylalanine, in the body. The first disease to be used for newborn screening.

PHEOCHROMOCYTOMA A small vascular tumor of the inner region of the adrenal gland. The tumor causes uncontrolled and irregular secretion of certain hormones.

PHILTRUM The center part of the face between the nose and lips that is usually depressed.

PHLEBOTOMY The taking of blood from the body through an incision in the vein, usually in the treatment of disease.

PHOBIA An exaggerated fear.

PHOSPHATE A substance composed of the elements phosphorus and oxygen that contributes to the hydroxyapatite crystals found in normal bones.

PHOSPHORYLATION The addition of phosphoric acid to another compound.

PHOTOPHOBIA An extreme sensitivity to light.

PHOTORECEPTORS Specialized cells lining the innermost layer of the eye that convert light into electrical messages so that the brain can perceive the environment. There are two types of photoreceptor cells: rod cells and cone cells. The rod cells allow for peripheral and night vision. Cone cells are responsible for perceiving color and for central vision.

PHOTOREFRACTIVE KERATECTOMY (PRK) A procedure that uses an excimer laser to make modifications to the cornea and permanently correct myopia. As of early 1998, only two lasers have been approved by the FDA for this purpose.

PHYTANIC ACID A substance found in various foods that, if allowed to accumulate, is toxic to various tissues. It is metabolized in the peroxisome by phytanic acid hydroxylase.

PHYTANIC ACID HYDROXYLASE A peroxisomal enzyme responsible for processing phytanic acid. It is abnormal in Refsum disease.

PICK'S DISEASE A rare type of primary dementia that affects the frontal lobes of the brain. It is characterized by a progressive loss of social skills, language, and memory, leading to personality changes and sometimes loss of moral judgment.

PITUITARY GLAND A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

PLACENTA The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

PLAQUES Abnormally deposited proteins that interfere with normal cell growth and functioning and usually progresses to cell death.

PLASMA The liquid part of the blood and lymphatic fluid that contains antibodies and other proteins.

PLASMA CELLS Antibody-secreting B-cells.

PLASMALOGENS Fat molecules that are important components of cells and of the myelin sheath that protects nerve cells.

PLASMAPHERESIS A procedure in which the fluid component of blood is removed from the bloodstream and sometimes replaced with other fluids or plasma.

PLASMIN The blood protein responsible for dissolving blood clots.

PLATELETS Small disc-shaped structures that circulate in the bloodstream and participate in blood clotting.

PLEURAL CAVITY Area of the chest occupied by the lungs.

PLEURITIS Inflammation of the pleura, the membrane surrounding the lungs.

PNEUMONIA An infection of the lungs.

PODIATRIST A physician who specializes in disorders of the feet.

POIKILODERMA A condition characterized by skin atrophy, widening of the small blood vessels (telangiectasia), and pigment changes giving a mottled appearance.

POLYDACTYLY The presence of extra fingers or toes.

POLYGENIC A trait, characteristic, condition, etc. that depends on the activity of more than one gene for its emergence or expression.

POLYHYDRAMNIOS A condition in which there is too much fluid around the fetus in the amniotic sac.

POLYMER A very large molecule, formed from many smaller, identical molecules.

POLYMORPHIC Describes a gene for which there exist multiple forms, or alleles.

POLYMORPHISM A change in the base pair sequence of DNA that may or may not be associated with a disease.

POLYMYOSITIS An inflammation of many muscles.

POLYP A mass of tissue bulging out from the normal surface of a mucous membrane.

POLYPECTOMY Surgical removal of polyps.

POLYPLOIDY A condition in which a cell receives more than two complete sets of chromosomes.

POLYPOSIS A descriptive term indicating that hundreds to thousands of polyps have developed in an organ.

POLYSACCHARIDE Linear or branched macromolecule composed of numerous monosaccharide (sugar) units linked by glycosidic bonds.

POLYSYNDACTYLY Having both extra digits (toes, fingers) as well as webbing (syndactyly) between the digits.

POOR MUSCLE TONE Muscles that are weak and floppy.

PORPHYRIN A large molecule shaped like a four-leaf clover. Combined with an iron atom, it forms a heme molecule.

PORT-WINE STAIN Dark-red birthmarks seen on the skin, named after the color of the dessert wine.

POSITIONAL CLONING Cloning a gene simply on the basis of its position in the genome, without having any idea of the function of the gene.

POSITIVE PREDICTIVE VALUE (PPV) The probability that a person with a positive test result has, or will get, the disease.

POSITIVE SYMPTOMS Symptoms of schizophrenia that are characterized by the production or presence of behaviors that are grossly abnormal or excessive, including hallucinations and thought-process disorder. DSM-IV subdivides positive symptoms into psychotic and disorganized.

POST-AXIAL POLYDACTYLY An extra finger or toe on the outside of the hand or foot.

POST-ICTAL STATE A period of lethargy, confusion, and deep breathing following a grand mal seizure that may last from a few minutes to several hours.

POSTERIOR FOSSA Area at the base of the skull attached to the spinal cord.

POVERTY OF SPEECH A negative symptom of schizophrenia, characterized by brief and empty replies to questions. It should not be confused with shyness or reluctance to talk.

PRADER-WILLI SYNDROME A syndrome caused by a deletion in the paternally inherited chromosome 15 or by uniparental disomy of the maternal chromosome 15.

PRE-AXIAL POLYDACTYLY An extra finger or toe on the inside of the hand or foot.

PREAURICULAR PITS Small pits in the skin on the outside of the ear.

PRECOCIOUS PUBERTY An abnormal condition in which a person undergoes puberty at a very young age. This condition causes the growth spurt associated with puberty to occur before the systems of the body are ready, which causes these individuals to not attain normal adult heights.

PREMUTATION A change in a gene that precedes a mutation; this change does not alter the function of the gene.

PRENATAL DIAGNOSIS The determination of whether a fetus possesses a disease or disorder while it is still in the womb.

PRENATAL TESTING Testing for a disease, such as a genetic condition, in an unborn baby.

PRIMARY ATRIAL SEPTATION An improper division of the atria of the heart, or a "hole in the heart," which results in the formation of a common atrium rather than the normal two-chambered atrium.

PRIMARY CANCER The first or original cancer site, before any metastasis.

PRIMARY CRANIOSYNOSTOSIS Abnormal closure of the cranial sutures caused by an abnormality in the sutures themselves.

PRIMARY DYSTONIA Dystonia that has no connection to disease or injury. Often hereditary.

PRIMARY IMMUNODEFICIENCY DISEASE (PID) A group of approximately 70 conditions that affect the normal functioning of the immune system.

PRIMARY POSITION, PRIMARY GAZE When both eyes are looking straight ahead.

PRIMARY TUMOR The organ or tissue where the tumor began.

PRION A term coined to mean "proteinaceous infectious particle." Prior to the 1982 discovery of prions, it was not believed that proteins could serve as infectious agents.

PROBAND The person in the family who is affected by a genetic disorder and who brings the family to the attention of a health care provider.

PROGERIA Genetic abnormality that presents initially as premature aging and failure to thrive in children.

PROGNATHISM A protruding lower jaw.

PROLACTIN A hormone that helps the breast prepare for milk production during pregnancy.

PROLIFERATION The growth or production of cells.

PROPHYLACTIC Preventing disease.

PROPIONIC ACID An organic compound that builds up in the body if the proper enzymes are not present.

PROPIONYL COA CARBOXYLASE An enzyme that breaks down the amino acids isoleucine, valine, threonine, and methionine.

PROPTOSIS Bulging eyeballs.

PROSTATECTOMY The surgical removal of the prostate gland.

PROTANOPIA The inability or difficulty in distinguishing blue and yellow colors.

PROTEASE An enzyme that acts as a catalyst in the breakdown of peptide bonds.

PROTEIN Important building blocks of the body composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

PROTEINURIA Excess protein in the urine.

PROTEOLIPID PROTEIN GENE (PLP) A gene that makes a protein that is part of the myelin in the central nervous system. Mutations in this gene cause PMD.

PROTO-ONCOGENE A gene involved in stimulating the normal growth and division of cells in a controlled manner.

PROTOPORPHYRIN A precursor molecule to the porphyrin molecule.

PROXIMAL Near the point of origin.

PROXIMAL MUSCLES The muscles closest to the center of the body.

PSEUDOAINHUM Constrictions of the skin seen in Vohwinkel disease that may lead to damage of the hands and feet and possible amputation of the affected areas.

PSEUDOCYST A fluid-filled space that may arise in the setting of pancreatitis.

PSEUDODEMENTIA A term for a depression with symptoms resembling those of dementia. The term dementia of depression is now preferred.

PSEUDODOMINANT A recessive trait that appears, in a pedigree analysis, to be a dominant trait.

PSEUDOTUMOR CEREBRI A syndrome of raised pressure within the skull that may cause vomiting, headache, and double vision.

PSORIASIS A common, chronic, scaly skin disease.

PSYCHODYNAMIC THERAPIES A form of psychological counseling that seeks to determine and resolve the internal conflicts that may be causing an individual to be suffering from the symptoms of depression.

PSYCHOLOGIST An individual who specializes in the science of the mind.

PSYCHOMOTOR Movement produced by action of the mind or will.

PSYCHOTHERAPY Psychological counseling that seeks to determine the underlying causes of a patient's depression. The form of this counseling may be cognitive/behavioral, interpersonal, or psychodynamic.

PSYCHOTIC DISORDER A mental disorder characterized by delusions, hallucinations, or other symptoms of lack of contact with reality. The schizophrenias are psychotic disorders.

PTERYGIUM COLLI Webbing or broadening of the neck, usually found at birth, and usually on both sides of the neck.

PTOSIS Drooping of the upper eyelid.

PUBERTY Point in development when the gonads begin to function and secondary sexual characteristics begin to appear.

PULMONARY ARTERY An artery that carries blood from the heart to the lungs.

PULMONARY ATRESIA When there is no valve between the right ventricle and the pulmonary artery (the artery leading from the heart to the lungs). In the absence of this valve, the blood does not flow into the lungs well.

PULMONARY EDEMA A problem caused when fluid backs up into the veins of the lungs. Increased pressure in these veins forces fluid out of the vein and into the air spaces (alveoli). This interferes with the exchange of oxygen and carbon dioxide in the alveoli.

PULMONARY HYPERTENSION A severe form of high blood pressure caused by diseased arteries in the lung.

PULMONARY STENOSIS Narrowing of the pulmonary valve of the heart, between the right ventricle and the pulmonary artery, limiting the amount of blood going to the lungs.

PUMICE STONE A small stone used to wear down thickened areas of the skin.

PUPIL The opening in the iris through which light enters the eye.

PUSTULE A pus-filled lesion of the skin that resembles the "pimples" of adolescent acne.

PYELONEPHRITIS Inflammation of the kidney commonly caused by bacterial infections.

PYGOPAGUS Conjoined twins who are joined back to back with fused buttocks.

PYLORIC SPHINCTER Circular smooth muscle found at the outlet of the stomach.

PYLORIC STENOSIS Narrowing of the stomach due to thickening of the pyloris muscle at the end of the stomach.

PYOGENIC Pus forming.

PYREXIA A medical term denoting fevers.

PYRIDOSTIGMINE BROMIDE (MESTINON) An anticholinesterase drug used in treating myasthenia gravis.

PYRUVATE CARBOXYLASE The enzyme responsible for the first step in the conversion of pyruvate molecules into glucose molecules. Individuals with type A PCD produce an highly inefficient form of pyruvate carboxylase. Individuals with type B PCD either completely lack the ability to produce this enzyme, or cannot produce it in sufficient quantities to sustain life.

PYRUVATE DEHYDROGENASE COMPLEX A series of enzymes and co-factors that allow pyruvate to be converted into a chemical that can enter the TCA cycle.

Q

QT INTERVAL The section on an electrocardiogram between the start of the QRS complex and the end of the T wave, representing the firing or depolarization of the ventricles and the period of recovery prior to repolarization or recharging for the next contraction.

QUADRIPLEGIA Paralysis of all four limbs.

R

RACHITIC Pertaining to, or affected by, rickets. Examples of rachitic deformities include curved long bones with prominent ends, a prominent middle chest wall, or bony nodules at the inner ends of the ribs.

RADIAL KERATOTOMY (RK) A surgical procedure involving the use of a diamond-tipped blade to make several spoke-like slits in the peripheral (non-viewing) portion of the cornea to improve the focus of the eye and correct myopia by flattening the cornea.

RADIATION High energy rays used in cancer treatment to kill or shrink cancer cells.

RADIATION THERAPY Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

RADICULOPATHY A bulging of disc material often irritating nearby nerve structures resulting in pain and neurologic symptoms. A clinical situation where the radicular nerves (nerve roots) are inflamed or compressed. This compression by the bulging disc is referred to as a radiculopathy. This problem tends to occur most commonly in the neck (cervical spine) and low back (lumbar spine).

RADIOLUCENT Transparent to x ray or radiation. The black area on x-ray film.

RANSON CRITERIA A system of measurements, including age and blood testing, used to predict the outcome of a person who has been hospitalized for an episode of pancreatitis.

RAYNAUD PHENOMENON/RAYNAUD DISEASE A condition in which blood flow to the body's tissues is reduced by a malfunction of the nerves that regulate the constriction of blood vessels. When attacks of Raynaud's occur in the absence of other medical conditions, it is called Raynaud disease. When attacks occur as part of a disease (as in scleroderma), it is called Raynaud phenomenon.

RECESSIVE Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

RECESSIVE GENE A type of gene that is not expressed as a trait unless inherited by both parents.

RECESSIVE TRAIT An inherited trait or characteristic that is outwardly obvious only when two copies of the gene for that trait are present.

RECTUM The end portion of the intestine that leads to the anus.

RECURRENCE RISK The possibility that the same event will occur again.

RECURRENT Tendency to repeat.

RED BLOOD CELLS Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

REDUCED PENETRANCE Failing to display a trait or disease despite possessing the dominant gene that determines it.

REFRACTION The bending of light rays as they pass from one medium through another. Used to describe the

action of the cornea and lens on light rays as they enter they eye. Also used to describe the determination and measurement of the eye's focusing system by an optometrist or ophthalmologist.

REFRACTIVE EYE SURGERY A general term for surgical procedures that can improve or correct refractive errors by permanently changing the shape of the cornea.

RENAL Related to the kidneys.

RENAL AGENESIS Absence or failure of one or both kidneys to develop normally.

RENAL CELL CARCINOMA A cancerous tumor made from kidney cells.

RENAL COLIC A spasmodic pain, moderate to severe in degree, located in the back, side, and/or groin area.

RENAL HYPOPLASIA Abnormally small kidneys.

RENAL SYSTEM The organs involved with the production and output of urine.

RENIN An enzyme produced by the kidneys.

RENPENNING SYNDROME X-linked mental retardation with short stature and microcephaly not associated with the fragile X chromosome and occurring more frequently in males, although some females may also be affected.

REPLICATE Produce identical copies of itself.

REPOLARIZATION Period when the heart cells are at rest, preparing for the next wave of electrical current (depolarization).

RESPIRATORY Having to do with breathing.

RETICULOCYTE Immature red blood cells.

RETINA The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

RETINAL DYSPLASIA Improper development of the retina that can lead to detachment of the retina.

RETINAL DYSTROPHY Degeneration of the retina, causing a decline in visual clarity.

RETINAL LACUNAE Small abnormal cavities or holes in the retina.

RETINAL PIGMENT EPITHELIUM (RPE) The pigmented cell layer that nourishes the retinal cells; located just outside the retina and attached to the choroid.

RETINITIS PIGMENTOSA Progressive deterioration of the retina, often leading to vision loss and blindness.

RETINOIDS A derivative of synthetic vitamin A.

RETINOPATHY Any disorder of the retina.

RHABDOMYOLYSIS Breakdown or disintegration of muscle tissue.

RHABDOMYOSARCOMA A malignant tumor of the skeletal muscle.

RHEUMATOID ARTHRITIS Chronic, autoimmune disease marked by inflammation of the membranes surrounding joints.

RHEUMATOID FACTOR Antibodies present in the majority of individuals with rheumatoid arthritis. A diagnostic marker for rheumatoid arthritis that is absent from ankylosing spondylitis and other seronegative spondyloarthopathies.

RHINITIS Infection of the nasal passages.

RHIZOMELIA A term used to describe the physical growth difference of short arms and legs.

RHIZOMELIC Disproportionate shortening of the upper part of a limb compared to the lower part of the limb.

RHO/RAC GUANINE EXCHANGE FACTOR Member of a class of proteins that appear to convey signals important in the structure and biochemical activity of cells.

RICKETS A childhood disease caused by vitamin D deficiency, resulting in soft and malformed bones.

RING CHROMOSOME An abnormal chromosome in which the terminal ends of the short (p) and long (q) arms have been lost and the remaining p and q arms subsequently join to form a ring.

ROD Photoreceptor that is highly sensitive to low levels of light and transmits images in shades of gray.

RUSSELL SYNDROME An alternative term for Russell-Silver syndrome. Many doctors use this term to mean an individual with Russell-Silver syndrome who does not have body asymmetry.

S

SACROILIAC JOINT The joint between the triangular bone below the spine (sacrum) and the hip bone (ilium).

SACROILIITIS Inflammation of the sacroiliac joint.

SADDLE NOSE A sunken nasal bridge.

SARCOIDOSIS A chronic disease characterized by nodules forming in the lymph nodes, lungs, bones, and skin.

SARCOPLASMIC RETICULUM A system of tiny tubes located inside muscle cells that allow muscles to contract and relax by alternatively releasing and storing calcium.

SATELLITES OF CHROMOSOMES Small segments of genetic material at the tips of the short arms of chromosomes 13, 14, 15, 21, and 22.

SAVANT SKILLS Unusual talents, usually in art, math, or music, that some individuals with autism have in addition to the deficits of autism.

SCAPHOCEPHALY An abnormally long and narrow skull.

SCAPULAR WINGING The jutting back of the shoulder blades that can be caused by muscle weakness.

SCINTIGRAPHY Injection and detection of radioactive substances to create images of body parts.

SCLERA The tough white membrane that forms the outer layer of the eyeball.

SCLERODERMA A relatively rare autoimmune disease affecting blood vessels and connective tissue that makes skin appear thickened.

SCLEROSIS Hardening.

SCOLIOMETER A tool for measuring trunk asymmetry; it includes a bubble level and angle measure.

SCOLIOSIS An abnormal, side-to-side curvature of the spine.

SCREENING Process through which carriers of a trait may be identified within a population.

SEBACEOUS Related to the glands of the skin that produce an oily substance.

SECOND-DEGREE RELATIVE Aunts, uncles, nieces, nephews, grandparents, grandchildren, and half siblings are second-degree relatives. These individuals have one fourth of their genes in common.

SECONDARY CRANIOSYNOSTOSIS Abnormal closure of the cranial sutures caused by a failure of the brain to grow and expand.

SECONDARY DYSTONIA Dystonia that occurs due to disease, injury, or another non-hereditary factor. Also known as symptomatic dystonia.

SEDATIVE Medication that has a soothing or tranquilizing effect.

SEIZURE Any unusual body function or activity that is under the control of the nervous system.

SEMEN A whitish, opaque fluid released at ejaculation that contains sperm.

SEMI-DOMINANT A trait expressed as a severe form in homozygous individuals and a milder form in heterozygous individuals.

SEMINAL VESICLES The pouches above the prostate that store semen.

SEMINEFEROUS TUBULES Long, thread-like tubes that are packed in areolar tissue in the lobes of the testes.

SENSITIVITY The proportion of people with a disease who are correctly diagnosed (test positive based on diagnostic criteria). The higher the sensitivity of a test or diagnostic criteria, the lower the rate of 'false negatives,' people who have a disease but are not identified through the test.

SENSITIZATION Change in immune system so that it identifies and "remembers" specific properties of an antigen.

SENSORINEURAL HEARING LOSS (SNHL) Sensorineural hearing loss occurs when parts of the inner ear, such as the cochlea and/or auditory nerve, do not work correctly. It is often defined as mild, moderate, severe, or profound, depending upon how much sound can be heard by the affected individual. SNHL can occur by itself, or as part of a genetic condition such as Pendred syndrome.

SENSORY NEURONS Class of neurons that specifically regulate and control external stimuli (senses: sight, sound).

SEPSIS An infection of the bloodstream.

SEPTAL Relating to the septum, the thin muscle wall dividing the right and left sides of the heart. Holes in the septum are called septal defects.

SEPTUM PELLUCIDUM A membrane between two of the normal cavities of the brain that prevents electrical signals from passing between different portions of the brain.

SERIAL CASTING A series of casts designed to gradually move a limb into a more functional position.

SEROLOGICAL Pertaining to serology, the science of testing blood to detect the absence or presence of antibodies (an immune response) to a particular antigen (foreign substance).

SEROSITIS Inflammation of a serosal membrane. Polyserositis refers to the inflammation of two or more serosal membranes.

SEROTONIN DOPAMINE ANTAGONIST (SDA) The newer second-generation antipsychotic drugs, also called atypical antipsychotics. SDAs include clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa).

SEROTYPE One form of a bacteria that has unique surface proteins. Each serotype causes a unique antibody response from a person's immune system.

SERUM The liquid part of blood, from which all the cells have been removed.

SERUM CK TEST A blood test that determines the amount of the enzyme creatine kinase (CK) in the blood serum. An elevated level of CK in the blood indicates that muscular degeneration has occurred and/or is occurring.

SERUM CREATININE A chemical in the urine of kidney patients used to determine kidney disease and failure. Elevated levels of serum creatinine are an early marker for severe kidney disease or failure.

SEVERE COMBINED IMMUNODEFICIENCY (SCID) A group of rare, life-threatening diseases present at birth, that cause a child to have little or no immune system. As a result, the child's body is unable to fight infections.

SEX CHROMOSOMES The X and Y chromosomes that determine the sex of an individual.

SEX-LINKED Related to either the X or the Y chromosome.

SEX-LINKED DISORDER A disorder caused by a gene located on a sex chromosome, usually the X chromosome.

SHOCK An inability to provide the body with the oxygen it requires, sometimes due to large amounts of bleeding or fluid loss.

SHORT RIB POLYDACTYLY SYNDROMES A collection of genetic disorders characterized by abnormally short ribs and extra fingers or toes. Research is ongoing to determine if these disorders are the result of mutations in a common gene.

SHORT STATURE Shorter than normal height, can include dwarfism.

SHUNT A small tube placed in a ventricle of the brain to direct cerebrospinal fluid away from the blockage into another part of the body.

SIALIC ACID N-acetylneuraminic acid, a sugar that is often at the end of an oligosaccharide on a glycoprotein.

SICKLE CELL A red blood cell that has assumed an elongated shape due to the presence of hemoglobin S.

SICKLE CELL ANEMIA A chronic, inherited blood disorder characterized by sickle-shaped red blood cells. It occurs primarily in people of African descent, and produces symptoms including episodic pain in the joints, fever, leg ulcers, and jaundice.

SIGMOIDOSCOPY The visual examination of the inside of the rectum and sigmoid colon, using a lighted, flexible tube connected to an eyepiece or video screen for viewing.

SILVER SYNDROME An alternative term for Russell-Silver syndrome. Many doctors use this term to mean an individual with Russell-Silver syndrome who also has body asymmetry.

SJÖGREN SYNDROME A chronic inflammatory disease often associated with rheumatoid arthritis.

SKELETAL DYSPLASIA A group of syndromes consisting of abnormal prenatal bone development and growth.

SKELETAL MUSCLE Muscles under voluntary control that attach to bone and control movement.

SKIN ERYTHEMA Irregular red streaks of skin.

SKIN HEMATOMA Blood from a broken blood vessel that has accumulated under the skin.

SLEEP APNEA Temporary cessation of breathing while sleeping.

SLEEP PARALYSIS An abnormal episode of sleep in which the patient cannot move for a few minutes, usually occurring on falling asleep or waking up. Often found in patients with narcolepsy.

SLY DISEASE Autosomal recessive metabolic disorder caused by dysfunction of the lysosomal enzyme beta-glucuronidase.

SMALL INTESTINE The part of the digestive tract between the stomach and the large intestine.

SMALL TESTES Refers to the size of the male reproductive glands, located in the cavity of the scrotum.

SOMATIC Relating to the nonreproductive parts of the body.

SOMATIC CELLS All the cells of the body except for the egg and sperm cells.

SOMATIC GENE THERAPY The introduction of genes into tissue or cells to treat a genetic related disease in an individual.

SOMATOSTATIN A body chemical, known as a cyclic peptide, involved in the release of human growth hormone from the pituitary gland.

SORE An open wound, bruise, or lesion on the skin.

SPASMODIC DYSPHONIA A focal dystonia that causes involuntary "spasms" of the vocal cords—leading to interruptions of speech and a decrease in voice quality.

SPASTIC A condition in which the muscles are rigid, posture may be abnormal, and fine motor control is impaired.

SPASTIC PARAPLEGIA Inability to walk, due to lack of proper neural control over the leg muscles.

SPASTICITY Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

SPECIFICITY The proportion of people without a disease who are correctly classified as healthy or not having the disease (test negative based on diagnostic criteria). The higher the specificity of a test or diagnostic criteria, the lower the number of 'false positives,' people who do not have a disease but who 'test' positive.

SPEECH THERAPIST Person who specializes in teaching simple exercises to improve speech.

SPERMATOZOA Mature male germ cells that develop in the seminiferous tubules of the testes.

SPHEROCYTES Red blood cells that are spherical in shape, as opposed to the normal bi-concave shape. Spherocytes are more rigid and their membranes are more fragile than normally-shaped red blood cells.

SPHINGOMYELIN A group of sphingolipids containing phosphorus.

SPHINGOMYELINASE Enzyme required to breakdown sphingomyelin into ceramide.

SPHYGMOMANOMETER An inflatable cuff used to measure blood pressure.

SPINA BIFIDA An opening in the spine.

SPINA BIFIDA OCCULTA The failure of vertebrae to close into the neural tube without nerves protruding. This is most often asymptomatic.

SPLAY Turned outward or spread apart.

SPLEEN Organ located in the upper abdominal cavity that filters out old red blood cells and helps fight bacterial infections. Responsible for breaking down spherocytes at a rapid rate.

SPLENIC FLEXURE The area of the large intestine at which the transverse colon meets the descending colon.

SPLENOMEGALY Enlargement of the spleen.

SPONDYLOARTHRITIS (SPONDYLITIS) Inflammatory disease of the joints of the spine.

SPONDYLOSIS Arthritis of the spine.

SPONGIFORM ENCEPHALOPATHY A form of brain disease characterized by a "sponge-like" appearance of the brain either on autopsy or via magnetic resonance imaging (MRI).

SPONTANEOUS Occurring by chance.

SPORADIC Isolated or appearing occasionally with no apparent pattern.

SPORADIC INHERITANCE A status that occurs when a gene mutates spontaneously to cause the disorder in a person with no family history of the disorder.

SPUTUM A mixture of saliva and mucus from the lungs.

STAGE The extent of a tumor. Tests will be done to determine if a tumor is localized to an organ or if it has spread to the lymph nodes and/or other organs. Treatment depends upon the stage of the cancer.

STAGING A method of describing the degree and location of cancer.

STATIC ENCEPHALOPATHY A disease of the brain that does not get better or worse.

STELLATE A star-like, lacy white pattern in the iris. Most often seen in light-eyed individuals.

STENOSIS The constricting or narrowing of an opening or passageway.

STETHOSCOPE An instrument used for listening to sounds within the body, such as those in the heart or lungs.

STILLBIRTH/STILLBORN The birth of a baby who has died sometime during the pregnancy or delivery.

STOMACH An organ that holds and begins digestion of food.

STRABISMUS An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

STROKE A sudden neurological condition related to a block of blood flow in part of the brain, which can lead to a variety of problems, including paralysis, difficulty speaking, difficulty understanding others, or problems with balance.

STROMA Middle layer of the cornea, representing about 90% of the entire cornea.

SUBARACHNOID SPACE The space between two membranes surrounding the brain, the arachnoid and pia mater.

SUBCORTICAL BAND HETEROTOPIA A mild form of lissencephaly type 1 in which abnormal bands of gray and white matter are present beneath the cortex near the ventricles.

SUBCORTICAL INFARCTS Obstruction of nerve centers below the cerebral cortex of the brain.

SUBMETACENTRIC Positioning of the centromere between the center and the top of the chromosome.

SUBSTANTIA NIGRA One of the movement control centers of the brain.

SUDDEN INFANT DEATH SYNDROME (SIDS) The general term given to "crib deaths" of unknown causes.

SULFATE A chemical compound containing sulfur and oxygen.

SUTURE "Seam" that joins two surfaces together.

SYMPHALANGISM Fusion of phalanges at their ends.

SYMPTOMATIC CARRIER A heterozygous person who carries a semi-dominant trait. This person experiences milder characteristics of this trait than a person who is homozygous or hemizygous in this trait.

SYNCHRONOUS Occurring simultaneously.

SYNCOPE A brief loss of consciousness caused by insufficient blood flow to the brain.

SYNDACTYLY Webbing or fusion between the fingers or toes.

SYNDROME A group of signs and symptoms that collectively characterize a disease or disorder.

SYNDROMIC HEARING LOSS Hearing loss accompanied by other symptoms that characterize a larger genetic syndrome of which hearing loss is just one of the characteristics.

SYNKINESIA Occurs when part of the body will move involuntarily when another part of the body moves.

SYNOPHRYS A feature in which the eyebrows join in the middle. Also called blepharophimosis.

SYNOVITIS Inflammation of the synovium, a membrane found inside joints.

SYRINGOMYELIA Excessive fluid in the spinal cord.

SYSTEMIC SCLEROSIS A rare disorder that causes thickening and scarring of multiple organ systems.

SYSTOLIC BLOOD PRESSURE Blood pressure when the heart contracts (beats).

T

TACHYCARDIA An excessively rapid heartbeat; a heart rate above 100 beats per minute.

TALIPES EQUINOVARUS A type of clubfoot characterized by a downward and inward pointing foot.

TAY-SACHS DISEASE An inherited biochemical disease caused by lack of a specific enzyme in the body. In classical Tay-Sachs disease, previously normal children become blind and mentally handicapped, develop seizures, and decline rapidly. Death often occurs between the ages of three to five years. Tay-Sachs disease is common among individuals of eastern European Jewish background but has been reported in other ethnic groups.

TCA CYCLE Formerly know as the Kreb's cycle, this is the process by which glucose and other chemicals are broken down into forms that are directly useable as energy in the cells.

TELANGIECTASIA An abnormal widening of groups of small blood vessels in the skin.

TELANGIECTASIS Very small arteriovenous malformations, or connections between the arteries and veins. The result is small red spots on the skin known as "spider veins".

TELANGIECTATIC A localized collection of distended blood capillary vessels.

TELESCOPING A term sometimes used to describe the relatively rapid progression of alcoholism in women, even though women usually begin to drink heavily at later ages than men do.

TELOGEN The resting phase of the hair growth cycle.

TENDON A strong connective tissue that connects muscle to bone.

TENOTOMY A surgical procedure that cuts the tendon of a contracted muscle to allow lengthening.

TENSILON TEST A test for diagnosing myasthenia gravis. Tensilon is injected into a vein and, if the person has MG, their muscle strength will improve for about five minutes.

TERATOGEN Any drug, chemical, maternal disease, or exposure that can cause physical or functional abnormalities in an exposed embryo or fetus.

TERATOGENIC Any agent that can cause birth defects or mental retardation in a developing fetus. Common teratogens are medications or other chemicals but they also include infections, radiation, maternal medical condition, and other agents.

TERATOGENIC FACTOR Any factor that can produce congenital abnormalities.

TERMINAL DELETION The abnormal early termination of a chromosome caused by the deletion of one of its ends.

TESTES The male reproductive organs that produce male reproductive cells (sperm) and male hormones.

TESTICLES Two egg-shaped glands that produce sperm and sex hormones.

TESTOSTERONE Hormone produced in the testicles that is involved in male secondary sex characteristics.

TETRALOGY OF FALLOT A congenital heart defect consisting of four (tetralogy) associated abnormalities: ventricular septal defect (VSD—hole in the wall separating the right and left ventricles); pulmonic stenosis (obstructed blood flow to the lungs); the aorta "overrides" the ventricular septal defect; and thickening (hypertrophy) of the right ventricle.

TETRAPHOCOMELIA Absence of all, or a portion of, all four limbs. The hands or feet may be attached directly to the trunk.

TETRAPLEGIA Paralysis of all four limbs. Also called quadriplegia.

TETRAPLOIDY A form of polyploidy; four sets of chromosomes.

THALASSEMIA An inherited group of anemias occurring primarily among people of Mediterranean descent. It is caused by abnormal formation of part of the hemoglobin molecule.

THALIDOMIDE A mild sedative that is teratogenic, causing limb, neurologic, and other birth defects in infants exposed during pregnancy. Women used thalidomide (early in pregnancy) in Europe and in other countries between 1957 and 1961. It is still available in many places, including the United States, for specific medical uses (leprosy, AIDS, cancer).

THERMOLABILE Heat-sensitive. A thermolabile protein is a protein that easily loses its shape when heated even only slightly.

THORACIC CAVITY The chest.

THORACOPAGUS Conjoined twins joined at the upper body who share a heart.

THROMBOCYTOPENIA A persistent decrease in the number of blood platelets usually associated with hemorrhaging.

THROMBOEMBOLISM A condition in which a blood vessel is blocked by a free-floating blood clot carried in the bloodstream.

THYMUS GLAND An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.

THYROID GLAND A gland located in the front of the neck that is responsible for normal body growth and metabolism. The thyroid traps a nutrient called iodine and uses it to make thyroid hormones, which allow for the breakdown of nutrients needed for growth, development, and body maintenance.

THYROID STIMULATING HORMONE (THYROTROPIN) A hormone that stimulates the thyroid gland to produce hormones that regulate metabolism.

THYROXINE (T4) AND TRIIODOTHYRONINE (T3) Thyroid hormones.

TIC Brief and intermittent involuntary movement or sound.

TISSUE Group of similar cells that work together to perform a particular function. The four basic types of tissue include muscle, nerve, epithelial, and connective tissues.

TONE A term used to describe the tension of muscles. Increased tone is increased tension in the muscles.

TONOMETER A device used to measure fluid pressures of the eye.

TORSADE DE POINTES A type of tachycardia of the ventricles that is characteristic of long-QT syndrome and Jervell and Lange Nielsen syndrome.

TORTICOLLIS Twisting of the neck to one side that results in abnormal carriage of the head and is usually caused by muscle spasms. Also called wryneck.

TORTUOUS Having many twists or turns.

TOXIC Poisonous.

TRABECULAR MESHWORK A sponge-like tissue that drains the aqueous humor from the eye.

TRACHEA Long tube connecting from the larynx down into the lungs, responsible for passing air.

TRACHEO-ESOPHAGEAL FISTULA Abnormal connection between the trachea and esophagus, frequently associated with the esophagus ending in a blind pouch.

TRACHEOSTOMY An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

TRACTION ALOPECIA Hair loss caused by pressure or tension on the scalp related to certain types of hair styles or equipment worn on the head.

TRAIT The set of physically observable characteristics that results from the expression of a gene.

TRANS-RECTAL ULTRASOUND A procedure where a probe is placed in the rectum. High-frequency sound waves that cannot be heard by humans are sent out from the probe and reflected by the prostate. These sound waves produce a pattern of echoes that are then used by the computer to create sonograms or pictures of areas inside the body.

TRANSCRIPTION The process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

TRANSCRIPTION FACTOR A protein that works to activate the transcription of other genes.

TRANSFERASES Family of enzymes that transfer a specific chemical group from one molecule to another.

TRANSFUSION The injection of a component of the blood from a healthy person into the circulation of a person who is lacking or deficient in that same component of the blood.

TRANSGENIC EXPERIMENT A genetic experiment in which a gene can be added to a laboratory animal's genetic material. The behavior of the altered animal can be compared with the behavior of an unaltered animal to help pinpoint the role of the gene affecting it.

TRANSLOCATION The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

TRANSMEMBRANE Anything that spans the width of a membrane.

TRANSPLANTATION The implanting of an organ from either a deceased person (cadaver) or from a live donor to a person whose organ has failed.

TRANSPOSITION OF THE GREAT ARTERIES A reversal of the two great arteries of the heart, causing blood containing oxygen to be carried back to the lungs and blood that is lacking in oxygen to be transported throughout the body.

TRANSVAGINAL ULTRASOUND A way to view the ovaries using sound waves. A probe is inserted into the vagina and the ovaries can be seen. Color doppler imaging measures the amount of blood flow, as tumors sometimes have high levels of blood flow.

TRANSVERSION A genetic term referring to a specific substitution of one base pair for another. There are only four possible tranversions: guanine for cytosine, cytosine for guanine, adenine for thymine, or thymine for adenine.

TRAUMA Injury.

TRICHOTILLOMANIA A psychiatric disorder characterized by hair loss resulting from compulsive pulling or tugging on one's hair.

TRIGGER DRUGS Specific drugs used for muscle relaxation and anesthesia that can trigger an episode of malignant hyperthermia in a susceptible person. The trigger drugs include halothane, enflurane, isoflurane, sevoflurane, desflurane, methoxyflurane, ether, and succinylcholine.

TRIGLYCERIDES Certain combinations of fatty acids (types of lipids) and glycerol.

TRIGONOCEPHALY An abnormal development of the skull characterized by a triangular shaped forehead.

TRIMESTER A three-month period. Human pregnancies are normally divided into three trimesters: first (conception to week 12), second (week 13 to week 24), and third (week 25 until delivery).

TRINUCLEOTIDE A sequence of three nucleotides.

TRINUCLEOTIDE REPEAT EXPANSION A sequence of three nucleotides that is repeated too many times in a section of a gene.

TRIOSE PHOSPHATE ISOMERASE Abbreviated TPI, this is the enzyme responsible for the conversion of dihydroxyacetone phosphate (DHAP) into D-glyceraldehyde-3-phosphate (GAP). DHAP and GAP are the two major products of a step in the multi-step process that converts glucose into ATP to supply the body with the energy it needs to sustain itself. Only GAP can continue in this process, but DHAP is produced in much higher quantities. People with TPI deficiency cannot change DHAP into GAP as efficiently as unaffected people, resulting in insufficient amounts of ATP from glucose to maintain normal cell function.

TRIPHALANGEAL THUMB (TPT) A thumb that has three bones rather than two.

TRIPLOIDY A form of polyploidy; three sets of chromosomes.

TRISOMY The condition of having three identical chromosomes, instead of the normal two, in a cell.

TRISOMY 18 A chromosomal alteration where a child is born with three copies of chromosome 18. This results in multiple birth defects and mental retardation.

TRUNCUS ARTERIOSUS Having only one artery coming from the heart instead of two. Often there is a ventricular septal defect (VSD) present.

TRYPSIN A digestive enzyme found in pancreatic fluid that breaks down proteins. This enzyme is abnormal in hereditary pancreatitis.

TRYPTOPHAN A crystalline amino acid widely distributed in proteins and essential to human life.

TUBULE A small tube lined with glandular epithelium in the kidney.

TUMOR An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

TUMOR SUPPRESSOR GENE Genes involved in controlling normal cell growth and preventing cancer.

TURNER SYNDROME Chromosome abnormality characterized by short stature and ovarian failure, caused by an absent X chromosome. Occurs only in females.

TYMPANOPLASTY Any of several operations on the eardrum or small bones of the middle ear to restore or improve hearing in patients with conductive hearing loss.

TYPE I INCONTINENTIA PIGMENTI Sporadic IP. This disorder is caused by mutations in the gene at Xp11. These mutations are not inherited from the parents, they are *de novo* mutations. This type of IP probably represents a different disease than type II IP.

TYPE II INCONTINENTIA PIGMENTI Familial, male-lethal, type IP. This type of IP is the "classic" case of IP. It is caused by mutations in the NEMO gene located at Xq28. Inheritance is sex-linked recessive.

TYROSINE An aromatic amino acid that is made from phenylalanine.

U

ULTRASONOGRAM A procedure where high-frequency sound waves that cannot be heard by human ears are bounced off internal organs and tissues. These sound waves produce a pattern of echoes, which are then used by the computer to create sonograms or pictures of areas inside the body.

ULTRASOUND An imaging technique that uses sound waves to help visualize internal structures in the body.

ULTRASOUND EVALUATION A procedure which examines the tissue and bone structures of an individual or a developing baby.

ULTRASOUND EXAMINATION Visualizing the unborn baby while it is still inside the uterus.

UMBILICAL HERNIA Protrusion of the bowels through the abdominal wall, underneath the navel.

UNDESCENDED TESTICLES Testicles that failed to move from the abdomen to the scrotum during the development of the fetus.

UNILATERAL Refers to one side of the body or only one organ in a pair.

UNIPARENTAL DISOMY Chromosome abnormality in which both chromosomes in a pair are inherited from the same parent.

UPSHOOT Upward movement of the eye.

UREA A nitrogen-containing compound that can be excreted through the kidney.

UREA CYCLE A series of complex biochemical reactions that remove nitrogen from the blood so ammonia does not accumulate.

UREA CYCLE DISORDER A disease caused by a lack of the enzyme that removes ammonia from the blood.

UREMIC POISONING Accumulation of waste products in the body.

URETERS Tubes through which urine is transported from the kidneys to the bladder.

URETHRA The tubular portion of the urinary tract connecting the bladder and external meatus through which urine passes. In males, seminal fluid and sperm also pass through the urethra.

URETHRITIS Inflammation of the urethra.

URINARY URGENCY An exaggerated or increased sense of needing to urinate.

URTICARIA Also known as hives. Usually associated with an allergic reaction.

UTERUS A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

UVEITIS Inflammation of all or part of the uvea, which consists of the middle vascular portion of the eye including the iris, ciliary body, and choroid.

V

VACCINE An injection, usually derived from a microorganism, that can be injected into an individual to provoke an immune response and prevent future occurrence of an infection by that microorganism.

VACUOLATION The formation of multiple vesicles, or vacuoles, within the cytosol of cells.

VARIABLE EXPRESSION Instances in which an identical genetic mutation leads to varying traits from affected individual to affected individual. This variance may occur between members of two separately affected families or it may occur between affected members of the same family.

VARIABLE EXPRESSIVITY Differences in the symptoms of a disorder between family members with the same genetic disease.

VARIABLE PENETRANCE A term describing the way in which the same mutated gene can cause symptoms of different severity and type within the same family.

VASCULAR Having to do with blood vessels.

VASCULAR MALFORMATION Abnormality of the blood vessels that often appears as a red or pink patch on the surface of the skin.

VAS DEFERENS The long, muscular tube that connects the epididymis to the urethra through which sperm are transported during ejaculation.

VASODILATOR A drug that relaxes blood vessel walls.

VECTORS Something used to transport genetic information to a cell.

VELLUS HAIRS The fine lighter-colored hairs that result from miniaturization.

VELO Derived from the latin word *velum*, meaning palate and back of the throat.

VENOUS THROMBOSIS A condition caused by the presence of a clot in the vein.

VENTILATOR Mechanical breathing machine.

VENTRAL WALL DEFECT An opening in the abdomen (ventral wall). Examples include omphalocele and gastroschisis.

VENTRICLE The fluid filled spaces in the center of the brain that hold cerebral spinal fluid.

VENTRICULAR SEPTAL DEFECT (VSD) An opening between the right and left ventricles of the heart.

VENTRICULOPERITONEAL SHUNT A tube equipped with a low pressure valve, one end is inserted into the lateral ventricles, the other end of which is routed into the peritoneum, or abdominal cavity.

VERMIS The central portion of the cerebellum, which divides the two hemispheres. It functions to monitor and control movement of the limbs, trunk, head, and eyes.

VERTEBRA One of the 23 bones that comprise the spine. *Vertebrae* is the plural form.

VERTEBRAL Related to the vertebrae.

VERY LONG CHAIN FATTY ACIDS (VLCFA) A type of fat that is normally broken down by the peroxisomes into other fats that can be used by the body.

VESTIBULAR NERVE The nerve that transmits the electrical signals collected in the inner ear to the brain. These signals, and the responses to them, help maintain balance.

VESTIBULAR SYSTEM A complex organ located inside the inner ear that sends messages to the brain about movement and body position. Allows people to maintain their balance when moving by sensing changes in their direction and speed.

VILLI Tiny, finger-like projections that enable the small intestine to absorb nutrients from food.

VISUAL ACUITY The ability to distinguish details and shapes of objects.

VISUAL CORTEX The area of the brain responsible for receiving visual stimuli from the eyes and integrating it to form a composite picture of an object.

VITAMIN DEFICIENCY Abnormally low levels of a vitamin in the body.

VOLUNTARY MUSCLE A muscle under conscious control, such as arm and leg muscles.

VOLVULUS A twisted loop of bowel, causing obstruction.

VON WILLEBRAND FACTOR (VWF) A protein found in the blood involved in the process of blood clotting.

W

WEYERS ACROFACIAL DYSOSTOSIS The condition resulting from a mutation of the same gene that shows mutation in Ellis-van Creveld syndrome. As is usually the case when comparing expressions of the same gene mutation, the single dose Weyers acrofacial dysostosis presents milder symptoms than the double dose Ellis-van Creveld syndrome.

WHIPPLE PROCEDURE Surgical removal of the pancreas and surrounding areas including a portion of the small intestine, the duodenum.

WHITE BLOOD CELL A cell in the blood that helps fight infections.

WHITE MATTER A substance found in the brain and nervous system that protects nerves and allows messages to be sent to and from the brain to various parts of the body.

WILSON DISEASE A rare hereditary disease marked by high levels of copper deposits in the brain and liver. It can cause psychiatric symptoms resembling schizophrenia.

WOLFFIAN DUCTS Structures in the embryo that develop into epididymides, vasa deferentia, and seminal vesicles in males.

WORD SALAD Speech that is so disorganized that it makes no linguistic or grammatical sense.

X

X CHROMOSOME One of the two sex chromosomes (the other is Y) containing genetic material that, among other things, determine a person's gender.

X INACTIVATION Sometimes called "dosage compensation". A normal process in which one X chromosome in every cell of every female is permanently inactivated.

X RAY An image of the body made by the passing of radiation through the body.

X RAYS High energy radiation used either to diagnose or treat disease.

X-LINKED GENE A gene found on the X chromosome.

X-INACTIVATION A condition in which one of the X chromosomes of a female is suppressed, or "turned off," in favor of the other X chromosome. Preferential X-inactivation is a process in which one X chromosome is inactivated in all the cells of the body, in preference to the other X chromosome. Females with preferential X-inactivation express X-linked traits as if they are hemizygous rather than homozygous or heterozygous.

X-LINKED Located on the X chromosome, one of the sex chromosomes. X-linked genes follow a characteristic pattern of inheritance from one generation to the next.

X-LINKED DOMINANT INHERITANCE The inheritance of a trait by the presence of a single gene on the X chromosome in a male or female, passed from an affected female who has the gene on one of her X chromosomes.

X-LINKED MENTAL RETARDATION Subaverage general intellectual functioning that originates during the developmental period and is associated with impairment in adaptive behavior. Pertains to genes on the X chromosome.

X-LINKED MUTATION An abnormal gene transmitted on the X chromosome.

X-LINKED RECESSIVE INHERITANCE The inheritance of a trait by the presence of a single gene on the X chromosome in a male, passed from his mother who has the gene on one of her X chromosomes. She is referred to as an unaffected carrier.

Z

ZYGOTE The cell formed by the uniting of egg and sperm.

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